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IN THIS ISSUE

FROM THE EDITOR

Sex differences in hypertension Where are we and where do we go from here?

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Dear reader,

Again, it is my pleasure to present a new double issue of Hypertension News to you (Opera 66-67). As before, it is a bit of a challenge to get the autumn issue out on time due to the long vacation periods, especially in Europe, starting in Mid-June in Scandinavia and finishing in Mid-September in the UK. We are delighted that the end of June issue (Opus 65) was downloaded by about 7,000 readers, which is higher than previous summer issues but lower than the ones published during the rest of the year. This is hardly surprising since most of us are on vacation during summer. I was recently asked how this figure is influenced if you download the Newsletter more than once. Well, normally it is not! If you use the same IP address you only score once.

Antihypertensive treatment in most hypertension guidelines do not differentiate the management of hypertension by sex, except for pregnancy specific recommendations, avoiding inhibitors of the renin-angiotensin system in women who are or are likely to become pregnant. This approach may miss some important issues, but to me it is unclear if, to date, there is any other evidence of clinically relevant sex differences with blood pressure lowering treatments.

In the "Learning the Ropes" section, six authors discuss sex differences in hypertension in a structured way, including evidence on the effectiveness of different antihypertensive treatments in women and men (page 13). These papers are introduced in two papers (page 9 - 11) by Dylan Burger (Canada) and Muscha Steckelings (Denmark)

The discussions differ from others by addressing regional differences when it comes to hypertension and risk: Ching Siew Mooi (Malaysia) provides an assessment from Asia, Lebo Gafane-Matemane (South Africa) shares the perspective on Africa, Karin Manhem (Sweden) focuses on Europe and the West, and Patricio Lopez-Jaramillo (Colombia) provides a Latin American view. From a mechanistic perspective, Eva Gerdts (Norway) provides an overview of sex differences in organ damage and pathophysiology. Finally, Nadia Khan (Canada) highlights the need for sex consideration in surveillance of hypertension, treatment initiation, and response to treatment.

Together these papers provide a contemporary view of the impact of sex on hypertension, which I recommend that you read to be able to provide the best possible care to women and men with hypertension worldwide. In this issue, there is also an interesting paper by Yoshihiro Kokubo (page 30), giving the Japanese perspective on the global burden of hypertension and cardiovascular disease, which I recommend you to read. To me, these nine papers clearly show how global the ISH has become in its approach to science!

Within a year, the new ISH Corporate Liaison Committee has been able to recruit three new corporate members and they strive for more! On page 43, the chairman of the committee, Thomas Unger presents the new ISH sponsors: ATTOQUANT Diagnostics (Austria), MERCK Kg aA (Germany), and AKTIIA (Switzerland).

Finally, I would also like to thank Giuseppe Mancia and the Milan group for their first-rate work with the Journal of Hypertension over many years. Giuseppe Mancia's "farewell" can be read in the latest issue of the journal (J Hypertens 2021;39:1731-32). The new editor Tony Heagerty, Manchester, UK is introduced on page 33 and he presents his new team on page 34 in this issue of the Newsletter.

Sincere thanks also to all the authors and to the lovely Hypertension News team.

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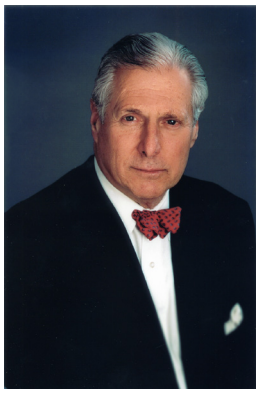

LEWIS LANDSBERG HAS LEFT US

LARS LINDHOLM
Editor

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Last week, Jill Landsberg gave me the sad news that Lewis Landsberg had died on Thursday 23 September in their summer home on the Cape, the place he loved so much. On behalf of the International Society of Hypertension (ISH) and the Hypertension News team, I express our deep condolences to Jill and the Landsberg family.

Lewis Landsberg graduated "Summa Cum Laude" from Williams College in 1960 and from Yale University School of Medicine in 1964. Following residency training in Internal Medicine at Yale-New-Haven Hospital, he had a research fellowship at the National Institute of Health (NIH) in the laboratory of Julius Axelrod (Nobel Prize Laureate). Lewis Landsberg was recruited to Harvard Medical School and promoted to Professor of Medicine in 1986. In 1999, he became the Dean of the Northwestern University, Feinberg School of Medicine in Chicago. In honor of Lewis Landsberg's accomplishments as Dean, the Deanship carries his name after he retired some years ago.

Lewis Landsberg served with great distinction on the Board of Management of the Journal of Hypertension for more than 25 years and was Chairman of the Board after he replaced John Chalmers in 1995–96, at the time when Alberto Zanchetti took over as Editor from John Reid.

I have had the privilege of working alongside Lewis on the Board first for the ESH and later for the ISH. With his polite, gentle and clever ways, his lovely sense of humor, and his "common sense" approach to difficult issues he stood out as an outstanding leader and a perfect chairman, whom I admired immensely. Rigmor and I have lost a close personal friend – we all owe Lewis a lot of thanks!

Northern LIghts (aurora borealis). Photo by Christer Andersson, Umeå, Sweden

Update from the Executive Committee

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While the summer holiday period is often a period of reduced activity, the ISH continues to roll along with several noteworthy activities.

The Mentorship and Training Committee (MTC) has been particularly active. On September 3rd the MTC hosted a training workshop on "Sex Differences in Hypertension" in partnership with the Women in Hypertension Research Committee. The event was attended by almost 300 people which is a tremendous success by any measure. For those who may have missed the event it will be available shortly on the ISH YouTube channel. Congratulations to Francine Marques and her committee on the tremendous success of this event. It is very exciting to see the emergence of this training program supporting knowledge and practical skill development. This will be a perfect compliment to their highly successful mentorship program. Speaking of the mentorship program. The executive has recently approved a "Mentee Handbook" for distribution. Stay tuned for its release in the coming months.

The MTC committee is not the only one that has been active, the Women in Hypertension Research Committee recently published its first newsletter. With the expansion of activities within this important community this should provide members with key updates on all activities in the society relevant for women in hypertension research. In addition, be sure to check out the first Cafe ISH video that was released on October 1. This is a new initiative from the Education Committee aimed at providing short, entertaining and educational videos on various topics in hypertension. Learn about the latest in hypertension research and management in the time it takes to drink your coffee.

August was also notable in the hypertension community for the release of the World Health Organization (WHO) Guidelines on the Pharmacological Treatment of Hypertension in Adults. As ISH Immediate Past-President Alta Schutte noted "On all global health fronts the recommendations of the WHO carry significant weight". To acknowledge this release members of the ISH Executive: President Maciej Tomaszewski, Secretary Bryan Williams, Immediate Past-President Alta Schutte, and Treasurer Fadi Charchar recorded a short supportive video. To further strengthen ties between ISH and the WHO the ISH executive is currently working towards recognition by WHO as a "non-state actor".

Elsewhere on the international front the ISH has contributed to an upcoming statement from the Global Coalition for Circulatory Health on Emergency Preparedness and Response for circulatory health care. Contributions from the ISH were from President Tomaszewski, Dr. Erika Jones (Communications Committee) and myself. The statement and associated advocacy campaign is set to be launched on October 12.

Finally, I note that the ISH is in the process of finalizing our trustees annual report to the UK Charity Commission. As a registered charity within the United Kingdom this is the means by which our society is held publicly accountable for how we have worked to carry out our mission. This report should be made public in the coming months and will be found on the UK Charity Commission web site once released.

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HOT OFF THE PRESS

Emerging evidence to start antihypertensive medication with low dose drug combinations

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The detection and treatment of hypertension remains inadequate in many countries, and patients treated for hypertension often do not reach recommended target blood pressure values[1]. Most of the effect on blood pressure reduction, and the lowest risk for side effects, occurs with low doses for most antihypertensive medications, suggesting that starting treatment with a combination of blood pressure lowering medicines at low doses may improve blood pressure control[2]. This concept is further supported by a recent study by Chow et al[3]. This randomised controlled parallel group multicentre study in Australia included 591 hypertensive patients with an untreated standard office blood pressure of 140–179 mm Hg systolic and/or 90–109 mm Hg diastolic (or daytime average ambulatory blood pressure of 135 and/or 85 mm Hg or above), or receiving monotherapy with a treated standard office blood pressure of 130–179 mm Hg systolic and/or 85–109 mm Hg diastolic (or daytime average ambulatory blood pressure of 125 and/or 80 mm Hg or above). Mean age was 59 years, 40% were female, 82% where white, and 50% were previously untreated; baseline standard office blood pressure was 153/89 mm Hg.

The participants were randomised double blind to a single pill low dose combination (irbesartan 37.5 mg, amlodipine 1.25 mg, indapamide 0.625 mg, and bisoprolol 2.5 mg) or initial monotherapy (irbesartan 150 mg). Amlodipine 5 mg was added at 6 weeks, with additional further drugs if required, to achieve a standard office blood pressure below 140/90 mm Hg. Primary outcome was the change in unattended office systolic blood pressure (OMRON HEM907 device) at 12 weeks.

The results[3] show a greater reduction in unattended office blood pressure by the single pill combination than by initial monotherapy (142/86 to 120/71 mm Hg vs 140/83 to 127/78 mm Hg), with a difference in unattended systolic blood pressure of -6.9 (95% confidence limits 4.9–8.9; $p<0.001$) mm Hg. Additional therapy was more common in the initial monotherapy group (40 vs 15%). The results were consistent across subgroups, for ambulatory and standard office blood pressures, and for systolic and diastolic blood pressures. The findings were maintained in favour of the single pill combination (-7.7, 5.2–10.3 mm Hg; $p<0.001$) during a 52 week follow up. There were no major differences in safety and tolerability between the two study groups.

Initiation of treatment with two or more medicines, as compared to monotherapy, improves drug and treatment adherence and persistence, reduce care provider inertia, improves blood pressure control, and reduces cardiovascular events; and single pill combinations appear to offer additional advantage[4-8]. The study by Chow et al[3] extend these findings by showing that a single pill low dose combination will achieve target blood pressure quicker and maintain blood pressure control more effectively than the prevailing practice to start with a single medicine, without major impairment of safety or tolerability. However, studies to demonstrate how blood pressure reduction with single pill low dose combinations translates into a superior reduction in cardiovascular morbidity and mortality are important. Also, the optimal combination of antihypertensive agents (numbers, classes, and doses) to include in a single pill low dose combination for best performance warrant further study. Of note, a similar strategy in the

management of chronic heart failure with reduced left ventricular ejection fraction to start treatment with several medicines simultaneously (i.e. an angiotensin converting enzyme-inhibitor or angiotensin receptor-neprilysin inhibitor, mineralocorticoid receptor-antagonist, beta-blocker, and a sodium-glucose co-transporter 2-inhibitor) is recommended in recent guidelines [9], and there is emerging evidence for a polypill concept (two or more antihypertensive agents plus statin, with or without thrombocyte inhibitor) in the primary prevention of cardiovascular disease [10]. These results may eventually change our management of high risk cardiovascular patients.

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Renal denervation reduces blood pressure in patients with treatment resistant hypertension

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Endovascular renal denervation has been investigated as a novel antihypertensive treatment option for hypertensive patients. Previous clinical trials in the absence or presence of antihypertensive therapy have shown significant blood pressure reductions after renal denervation [1]. In particular, the RADIANCE-HTN SOLO trial [2], showed the efficacy of renal denervation in patients with mild to moderate hypertension off-antihypertensive treatment during the initial 2-month trial period, with blood pressure lowering effect maintained at 6- and 12-month post-intervention when patients were put back on medications. The RADIANCE- HTN TRIO [3] trial aimed to assess the efficacy and safety of endovascular ultrasound renal denervation in patients with treatment resistant hypertension and to overcome previous methodological limitations in studies addressing renal denervation in this category of patients.

RADIANCE-HTN TRIO is a randomised, international, multicentre, single-blind trial in which 53 centres in Europe and USA, led by Michel Azizi from the Hôpital Européen Georges Pompidou, AP-HP in Paris, France, and Ajay Kirtane from Columbia University Medical Center/ New York-Presbyterian Hospital, NY, USA, enrolled 989 participants with treatment resistant hypertension aged 18-75 years with office blood pressure > 140/90 mmHg on three or more antihypertensive medications including a diuretic. Patients were switched to a once-daily single pill combination of a calcium channel blocker, an angiotensin-receptor blocker and a thiazide diuretic. After four weeks, 136 patients (80% men, mean age 52 years) with blood pressure ≥135/85 mmHg were randomly assigned to endovascular ultrasound renal denervation or a sham procedure. The primary endpoint was the change in daytime ambulatory systolic blood pressure at 2 months. Full drug adherence to the combination therapy at two months, monitored by urine toxicological measurements, was high and similar in the two groups (82%). After two months of follow-up, the daytime ambulatory systolic blood pressure was significantly reduced by 8 mmHg in the denervation group, compared to the sham group (–3.0 mmHg; median between- group difference –4.5 mmHg, 95% CI –8.5 to –0.3 mmHg, adjusted p = 0.022). Changes of other blood pressure parameters were also in favour of renal denervation, including a significant reduction in 24-h ambulatory blood pressure, night-time ambulatory systolic blood pressure, and office and home systolic blood pressures. Moreover, 35% of patients whose blood pressure was not controlled at randomisation had blood pressure normalisation two months after renal denervation compared to 21% in the in the sham group.

This study shows that ultrasound renal denervation significantly reduced blood pressure in patients with treatment resistant hypertension. Importantly, the study was designed to overcome potential biases and limitations. By using a single-pill triple combination and reducing pill burden, a high adherence to standard treatment was obtained. The blood pressure reductions observed in the RADIANCE-HTN TRIO trial are of a magnitude previously associated with a reduction in stroke, coronary heart disease, heart failure and all-cause mortality [4], which, if confirmed over the long term, may significantly reduce the cardiovascular burden in this high risk population. A follow-up at 6, 12 and 36 months is currently ongoing and will provide important information on the long-term effects of renal denervation and blood pressure reduction. Together with previous studies, these results suggest that catheter-based renal

denervation efficiently lowers blood pressure across the spectrum of hypertension severity, possibly providing an alternative treatment option in high-risk patients with hypertension.

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CALL FOR BIDS

INTERNATIONAL SOCIETY OF HYPERTENSION 2026 BIENNIAL SCIENTIFIC MEETING

The Council of the International Society of Hypertension (ISH) would like to invite scientists, research groups or national societies with an interest in hypertension to host the **ISH Biennial Scientific Meeting in 2026.**

Bid Deadline is Wednesday 1st March 2022

ISH particularly encourages submissions from regions that have not hosted ISH Biennial Scientific Meetings before.

Criteria

1. Quality and quantity of available convention centre space.
2. International air accessibility and cost.
3. Quality, quantity and type of hotel rooms available withinclose proximity of the convention centre.
4. Incentive appeal of city for international attendees.
5. Innovative / new programme features.
6. Support of national hypertension related society.
7. Support of related national hypertension societies /organisations in the region.
8. Commitment from local hypertension experts.
9. Experience of host organisation with similar meetings.
10. Financial resources available to host the meeting.
11. Quality and experience of PCOs (Professional Conference Organisers) and similar organisations to assist in the organisation and delivery of the conference.
12. Meetings should ideally be hybrid to allow remote participation and offer a number of free to view lectures.

DELEGATE PROFILE

The congress typically attracts delegates from over **60 countries worldwide.** Participants comprising of hypertension specialists, cardiologists, nephrologists, general practitioners, scientists, nurses, allied health care professionals, patients and patient group representatives.

Financial Liability

Local organisers must sign a contract committing to pay ISH one half of the surplus income. The ISH does not assume responsibility for any loss associated with the event.

Format of Proposals

Please note that only electronic proposals will be accepted and not paper versions. Proposals should be as complete as possible, addressing all items as outlined in this document and indicated in the 'ISH Guidelines for future organisers' document. Bids should be accompanied by at least one set of floor plans of the proposed convention centre indicating the proposed space to be used for the ISH Biennial Scientific Meeting.

For the full guideline document
and any questions regarding this, please contact:

ISH Secretariat
Email: helen@ish-world.com
Web: www.ish-world.com

SUBMISSION TIMETABLE

- **Bid Deadline 1st March 2022**
- Notification of Shortlisted Candidates Wednesday 1st June 2022
- Presentations of shortlisted bids to ISH Bidding Review Committee at ISH Kyoto 2022 in October 2022
- Announcement of 2026 Congress host November 2022

LEARNING THE ROPES: ASPECTS ON MALE VS. FEMALE SEX IN HYPERTENSION

Introduction 1

Sex and Gender-Based Analysis in Hypertension: Known knowns, the known unknowns, and the unknown unknowns

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The past year has been particularly noteworthy in terms of sex- and gender-based research in hypertension. In May, the Lancet Women and Cardiovascular Disease Commission released their report and call to action which included recommendations to reduce the global burden of cardiovascular disease in women by 2030 [1]. Within the ISH, there has been a significant increase in activity from our Women in Hypertension Research Committee and the ISH Mentorship and Training Committee recently hosted a training workshop on "Sex Differences in Hypertension". It is therefore timely that Hypertension News would feature this Learning the Ropes on Aspects of male vs. female sex in hypertension.

Sex- and gender-based analysis (SGBA) is an approach to systematically examine sex (i.e. biological factors) and gender (i.e. sociocultural factors)-based differences in measured variables between men, women, boys, girls and gender-diverse people. The central goal is to ensure rigorous research that achieves a more complete understanding of the health determinants for all peoples. SGBA has, in fact, been a consideration in hypertension research for some time; Boynton and Todd noted that male university students had higher BPs compared with women in 1947 and animal data supporting this from the late 1980s [2,3]. However, as elegantly noted by Dr. Steckelings in her accompanying introduction, the relationship is more complex, particularly in later life.

This Learning the Ropes feature aims to outline the evidence for sex/gender differences in hypertension incidence and pathogenesis. Importantly, it distinguishes itself from other such discussions by addressing regional considerations: Ching Siew Mooi (Malaysia) provides a perspective from Asia, Lebo Gafane-Matemane (South Africa) shares the perspective of Africa, Karin Manhem (Sweden) focus on Europe and Patricio Lopez-Jaramillo (Colombia) provide a Latin American perspective. Important regional differences are highlighted: for example Dr. Gafane-Matemane highlights that in certain regions of Africa the prevalence of hypertension is higher in women than men. The authors also offer insights into region-specific sociocultural factors that may contribute to differences. Dr. Manhem notes better blood pressure control in younger ages in women and suggests that this may indicate sex/gender differences in care.

From a mechanistic perspective, Dr. Eva Gerdts (Norway) provides an overview of sex/gender differences in organ damage and pathophysiology. In particular she discusses sex differences in left ventricular hypertrophy which she notes is "more prevalent and less modifiable by treatment in women than men" as well as arterial remodeling. Learning the ropes concludes with a look forward to translating evidence of sex differences in hypertension to clinical care. Dr. Nadia Khan (Canada) highlights the need for sex consideration in surveillance of hypertension, treatment initiation, and response to treatment.

Together these works provide a contemporary view of the impact of sex/gender on hypertension. This goes well beyond existing contributions that are often highly descriptive in nature. However, as each contribution notes, there remains a paucity of information to guide clinical management. Dr. Khan notes that "Clinical trial inclusion of women has been historically poor, and largely focused on Western populations…". From a population health standpoint Dr. Lopez-Jaramillo notes that in Latin American countries "Improving hypertension management, particularly in youth male, will require understanding context-specific barriers that limit care and system-level changes directed at overcoming these barriers". I would add that the majority of studies, particularly those focused on pathophysiology are focused on sex differences and that our appreciation of the role of gender is far less advanced. Nevertheless, work continues in

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this area and better understanding of the influence of sex and gender on hypertension should ultimately lead to improved care for all men, women, boys, girls and gender-diverse individuals.

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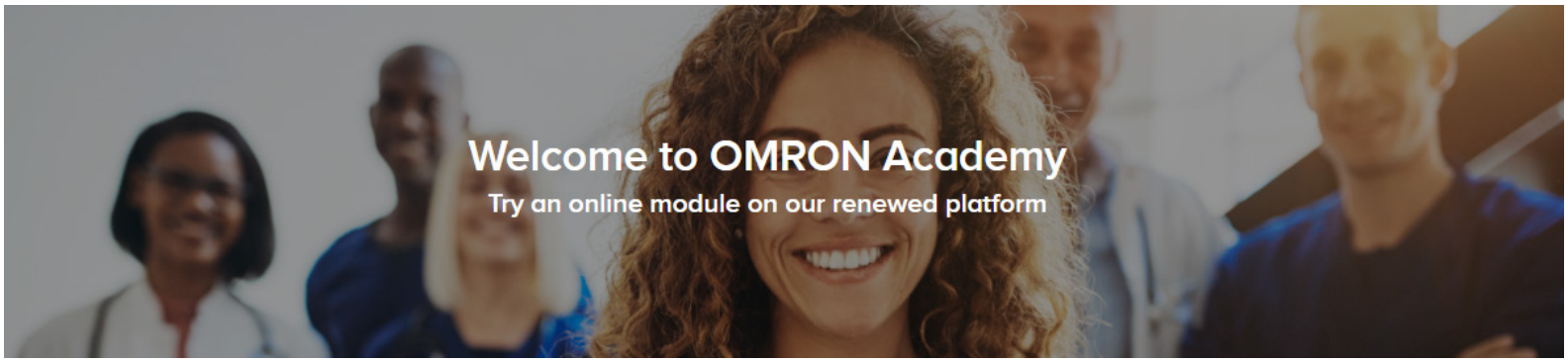

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LEARNING THE ROPES: ASPECTS ON SEX AND GENDER

Introduction 2

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Sex differences in hypertension have for a long time been neglected in all areas of hypertension research including basic and clinical science. This general approach has been changing over the past years. Important drivers of this change have been new rules by many funding agencies and by regulatory authorities, which demand the inclusion of subjects or animals of both sexes in preclinical and clinical studies. The change is also owed to the continuous work by individual researchers and societies for raising awareness of the existence and importance of sex differences in pathophysiology, prevalence, diagnosis, awareness, treatment (incl. side effects), and long-term consequences of hypertension.

One of the more recent, important insights from epidemiological studies on sex differences in hypertension is the fact that although prevalence of hypertension is higher in men than women of younger and middle age, this reverses from the 7th decade of life, from when hypertension rates in women exceed those in men [1]. Moreover, higher BP levels in elderly women go hand in hand with a higher risk of stroke than in males of the same age group. Of note, the increase in the risk of stroke with higher BP levels is almost twice as strong in women as it is in men [2].

Obviously, the steep increase in hypertension prevalence in women between menopause and the age of 70 strongly points to a causative role of hormones. It is indeed beyond question that several hormonal systems, which are involved in the regulation of BP, are under the control of sex hormones in men and women [3] . These include effects of oestrogen and androgens on the renin-angiotensin-system, the sympathetic nervous system, endothelin, vasopressin, nitric oxide and also the immune system [4].

Furthermore, hypertension-induced end-organ-damage has been recognised to be dependent not only on pressure-overload, but also on a series of other contributing factors, many of which are sex dependent as lined out by Eva Gerdts and Helga Midtbø in their article on "Organ damage and pathophysiology" for this issue of "Learning the Ropes".

Despite the unquestionable progress of recent years in basic and clinical research on sex differences in hypertension, recommendations in major hypertension guidelines from the leading societies worldwide are still widely sex neutral due to a lack of evidence from clinical trials as pointed out by Nadia Khan in her article on "Sex Differences in Antihypertensive Treatment". Even the SPRINT study, which compared standard with intensified (systolic BP goal < 120 mmHg) treatment of hypertension, failed in enrolling 50% women as planned, but included only 36%, and was therefore underpowered for this patient group [5]. Nevertheless, two sub-group analyses were published comparing the outcome in women and men in SPRINT but with contrasting results. This again underlined that SPRINT results are inconclusive for women and that a sex-neutral implementation of SPRINT results into guidelines should be regarded with caution [6–8].

The same limitations in terms of evidence apply to recommendations on the management and treatment of preeclampsia in major guidelines, which refer back to underpowered clinical trials resulting in low-evidence recommendations based on expert opinion as for example pointed out in the WHO guidelines [9,10]. Furthermore, it was only recognised quite recently that women with a history of gestational hypertension have an increased lifetime risk for CV events [11,12], which is another aspect that needs more research, awareness and more consideration in guideline recommendations.

While sex differences are one determinant of the many aspects of hypertension as outlined above, the articles by Lebo Gafane-Matemane and Julia Kagura (Sex Differences in the Epidemiology of Hypertension: The African Perspective), by Patricio Lopez-Jaramillo and Maria Angelica Chacon (The Latin American Perspective), by Ching Siew Mooi, Navin Kumar Devaraj and Lee Kai

Wie (The Asian Perspective) and by Karin Manhem, John – Emil Bager and Charlotta Ljungman (The Western Perspective) document impressively that ethnicity, socioeconomic conditions, education, geography and other life circumstances have an impact on prevalence, awareness and treatment/control of hypertension as well, and that research needs to be intensified in an effort to better understand how all of the confounding factors come together and how we best consider them to provide the best possible care to male and female patients worldwide.

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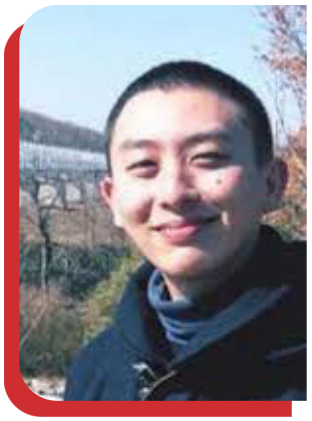
LEARNING THE ROPES: ASPECTS ON MALE VS. FEMALE SEX IN HYPERTENSION

Epidemiology and risk: Asian perspective



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Hypertension is one of the important medical conditions that is attributed to premature death due to cardiovascular disease (CVD) globally. Generally, premenopausal women have a lower risk of hypertension and cardiovascular disease compared with age-matched men but this advantage for women gradually disappears after they attained menopause. At ages of 65 years and above, a higher percentage of women have hypertension and CVD compared with men, and the gap will likely increase with the continued aging of the female population [1, 2].

The risk of cardiovascular disease in women is often overlooked due to the misunderstanding that women are more 'protected' than men against CVD[2]. The inattention of CVD in women may lead to less aggressive clinical management. Among female who die, one third of them actually succumb to coronary heart disease (CHD). Studies have reported that female patients with CHD have a poorer control of cardiovascular risk factor profiles as compared to male [2].

There are gender differences in terms of risk factors for cardiovascular disease development. Men is greatly affected by conventional risk factors like age, hypertension, total cholesterol and low-density lipoprotein (LDL)-cholesterol.[2] On the other hand, women are affected by other risk factors like smoking, diabetes, triglyceride and high-density lipoprotein (HDL)-cholesterol levels [2]. On top of that women with underlying pregnancy induced hypertension, preeclampsia, gestational diabetes mellitus and polycystic ovary syndrome are at higher risk of developing cardiovascular disease[2].

In Asia, the prevalence of hypertension and CVD in men is higher compared with females. In China, the overall prevalence of hypertension was 23.2% with 24.5% in men versus 21.9% in females[3].

Besides sex difference on biological and behavioural risk factors for CVD, gender-related differences also occur in social, education, environmental and support system that attribute to the development of hypertension particularly in Asia. Studies reported women in lower socioeconomic and education groups had a higher prevalence of hypertension compared with men[4]. This could be due to the fact that women with lower socioeconomic and education groups were most likely divorced, had poor social support, poor dietary habits, stress, depression and no access to health services. Even though some of them also work as labourers, the demand for physical activity is low and this tend to lead to a sedentary lifestyle [4]. All these contributed to a higher prevalence of hypertension in women with a poor socioeconomic background.

Contrasting findings are found in men whereby having a medium income and low education level were the protective factors for men against development of hypertension [4, 5]. This could be due to the fact that men with a low education level usually worked as a labourer and were performing higher levels of physical activity and therefore, were less likely to have hypertension. Another important finding reported in the literature includes those men suffering from depression were at risk of having hypertension and this could be explained by the fact that depression could lead to the overstimulation of the sympathetic nervous system [4].

Thus, a gender-specific approach for hypertension prevention programmes must be carried out in an Asian context to cater for the differences in gender, particularly providing social support to those vulnerable groups particularly to women in order to have a more effective health promotion outcomes. During daily clinical practice, clinicians should be aware of gender differences in hypertension risk factors in conjunction with the annual blood pressure screening programme and provide gender-based health advice to the public. Similarly, health education at the community level should be gender specific and avoid one-size-fits-all content, since the risk factors are different for men and women as evidenced by the above discussion.

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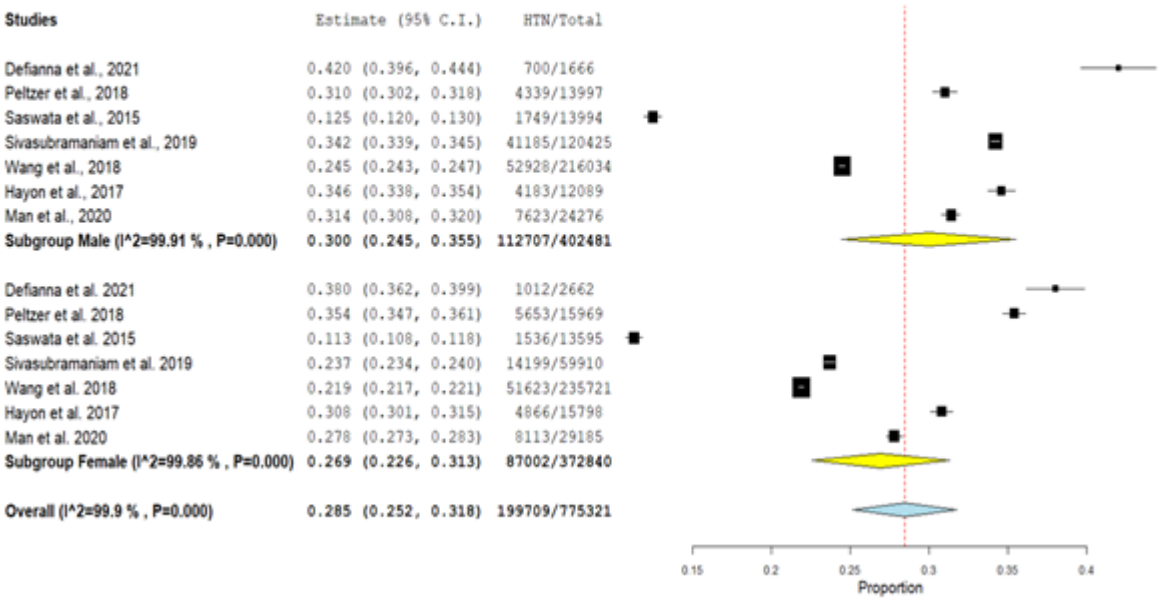
Table 1. Prevalence of hypertension according to gender distribution

				Number of participants			Prevalence of hypertension, %		
Author	year	Country	Design	Overall	Male	Female	Overall	Male	Female
Defianna SR	2021	Indonesia	Cross-sectional	4328	1666	2662	40.0	42.0	38.0
Peltzer K	2018	Indonesia	Cross-sectional	29965	13997	15969	33.4	31.0	35.4
Saswata G	2015	India	Cross-sectional	27 589	13 994	13 595	-	12.5	11.3
Sivasubramaniam R	2019	India	Cross-sectional	180335	120425	59910	30.7	34.2	23.7
Wang ZW	2018	China	Cross-sectional	451755	216034	235721	23.2	24.5	21.9
Hayon MC	2017	Korea	Cross-sectional	27887	12089	15798	-	34.6	30.8
Man JS	2020	Malaysia	Cross-sectional	241796	24276	29185	29.7	31.4	27.8

Figure 1: Meta-analysis for Prevalence of hypertension by gender



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LEARNING THE ROPES: ASPECTS ON MALE VS. FEMALE SEX IN HYPERTENSION

Epidemiology and risk: Western perspective



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Hypertension is a widespread condition which is associated with a well-known risk of cardiovascular disease and premature death. At the same time, treatment of hypertension is well-established, and we can choose between several evidence-based treatment strategies.

Cardiovascular disease plays a major role for both men and women, but women are affected later in life than men are [1]. Women are also exposed to gender specific conditions such as preeclampsia and hypertension during treatment with oral contraception.

This begs the question: Is the development of increased blood pressure different between the genders and is treatment and control of high blood pressure diverse with respect to gender? Furthermore, what is specific regarding the European perspective?

In a recently published, comprehensive, pooled analysis from 1200 studies in 184 countries covering 99 % of the world's population, the prevalence, detection, treatment, and control of hypertension were presented [2]. The authors analyzed data on blood pressure levels and treatment from 1990 to 2019 in individuals aged 30–79 years in population-representative studies. More women than men were diagnosed with hypertension and the number of individuals with hypertension doubled during the time period. When focusing on high-income western countries, women in younger ages more often had well-controlled hypertension compared to men in 2019, with a shift towards better control in men in older ages. During the investigated time period, the rate of controlled hypertension increased for both genders, but more so in women. Despite these improvements, the rate of well-controlled hypertension only reached an unimpressive 50% in women in 2019. There were also relatively large differences within Europe, and even more within different regions characterized as high-income western countries. For example, Canada displayed high rates of individuals with well-controlled blood pressure. Earlier this year, we presented data on 8-year trends in blood pressure and lipid-levels in a primary-care setting in a region in Sweden (n=259 753). In patients with a diagnosis of hypertension, but without ischemic heart disease or diabetes mellitus, the rate of blood pressure control increased from approximately 40 % to 50 % in 2017 without any detectable difference between the genders [3]. The rate of lipid-level control barely improved at all during the same period.

It is interesting to compare countries and regions with similar socioeconomic structure and insurance and welfare systems. For example, how does Canada manage to attain target blood pressures to a greater extent than Sweden? Why do younger women in Europe more often have higher rates of well-controlled blood pressure compared to men of the same age? When health care and medication is publicly funded, which strategy is the best? This begs the question of how we should organize the detection and care of individuals with increased blood pressure? This is a field of research where we at present do not have any convincing evidence of the best way to act. We have shown that blood pressure control was better in patients with hypertension when antihypertensive treatment was managed primarily by specially trained nurses, compared to when antihypertensive treatment was managed by physicians [4]. In another study, we also found that female physicians more often appear to reach the treatment goal for blood pressure in female patients [5].

The options today are plentiful; single-pill/poly-pill, opportunistic screening, home monitoring/office blood pressure, self-monitoring/health care professionals, physicians/nurses, telemonitoring/individual meeting with health professional? The questions are many, the answers are diverse.

In conclusion, hypertension in Europe (and the rest of the world) has increased over the last decades. The number

of individuals with well-controlled blood pressure has also increased to some extent, but insufficient treatment control and the unnecessary and avoidable cardiovascular disease which it results in, is still a challenge to the health care system. There is no evidence supporting a specific treatment strategy regarding women, but a better blood pressure control in younger ages in women could indicate that there exist some differences between the care of patients with hypertension.

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LEARNING THE ROPES: ASPECTS ON MALE VS. FEMALE SEX IN HYPERTENSION

Epidemiology and risk: African perspective

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Hypertension remains a major public health concern in Africa, with countries in sub-Saharan Africa (SSA) among those with the lowest levels of detection, treatment and control globally [1]. A study across four countries reported the highest prevalence in South Africa (range across sites: 41.6%-54.1%) and the lowest in Burkina Faso (15%). Hypertension prevalence increased with age in both men and women. Overall, the prevalence of hypertension was higher in women (35%) than in men (31%), a pattern also observed with awareness levels (53.8% vs 39.4%) and rates of control (51% vs. 39%) [2]. In half of the sites, of which two were in South Africa (rural) and one in Kenya (informal settlement), the prevalence of hypertension was higher in women as compared to men, while in Burkina Faso, the prevalence was higher in men as compared to women [2]. Some of the age differences in hypertension prevalence by sex were attributed to obesity and physical inactivity. Recent data from Sierra Leone showed similar hypertension prevalence between men (21%) and women (22%) [3]. However, when considering middle-aged and older individuals, the prevalence was higher in women (48%) than in men (35%). This implies that social and biological factors acting at different stages of the life course may be the underlying determinants in the sex-specific discrepancies in hypertension.

The high prevalence and awareness levels in women were also evident in a nation-wide study conducted in Nigeria, while treatment and control rates were similar between men and women. Individuals living in urban areas had higher rates of awareness and treatment than those in rural areas [4]. Similarly, in Sierra Leone [3], awareness, treatment and control rates were higher in urban than rural areas and differed by education level. Another multi-country study, which included only hypertensive patients from 12 countries in SSA confirmed the high burden of hypertension in women and similar treatment and control rates between men and women [5]. Of note, women in this study had a higher frequency of other cardiovascular risk factors such as obesity, sedentary lifestyle and family history, but less cardiovascular complications as compared to men [5].

Modifiable and non-modifiable risk factors contribute to the burden of hypertension in African populations. Low socioeconomic status, older age, urbanization, level of education, tobacco use, excessive alcohol consumption, physical inactivity, overweight and obesity, diet (high salt intake) are major risk factors for hypertension in SSA (Figure 1) [2, 3, 6]. Living in a rural area and lack of health insurance are among the barriers to screening, treatment and control [4-5]. Early life factors such as low birth weight and childhood obesity, and ethnicity/race are associated with early onset of hypertension and are influenced by socioeconomic disparities in some SSA countries such as South Africa [7]. Risk factors such as obesity and physical inactivity were found to be prominent in women, while smoking and alcohol consumption are common in men and increasing in young adults. Therefore, health education and promoting change in behaviour can significantly reduce the risk of developing hypertension.

In Africa, the burden of hypertension and sex differences in detection, treatment and control rates differ by region and locality (rural/urban). The low levels of awareness, treatment and control highlight the need for intensified screening efforts and implementation of cost-effective and context-specific hypertension management strategies, such as health education, lifestyle

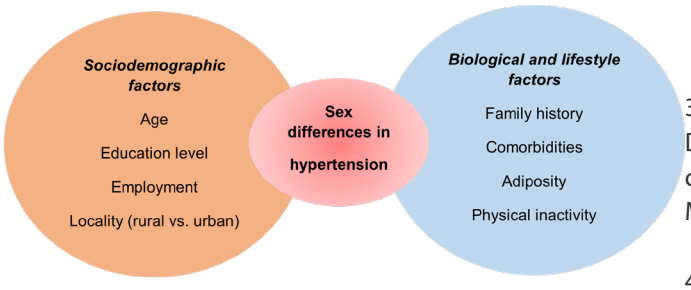

Figure 1: Contributing factors to the burden of hypertension in sub-Saharan Africa

modifications and improving access to medicines. It is equally important to investigate pathophysiological mechanisms underlying sex differences in hypertension development in African populations to enhance understanding and management of hypertension.

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LEARNING THE ROPES: ASPECTS ON MALE VS. FEMALE SEX IN HYPERTENSION

Epidemiology and risk: Latin - American perspective

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Cardiovascular disease (CVD) is the major cause of death in Latin American countries (LATAM) and hypertension is the risk factor with the higher population attributable fraction (PAF) [1]. The Prospective Urban Rural Epidemiology (PURE) study has collected extensive data on the prevalence, awareness, treatment and control of hypertension in rural and urban communities in Argentina, Brazil, Chile Colombia, Peru and Uruguay [2]. The mean age of the study population was 51.7 (9.7) years, 60% were female, and 32.1% belonged to rural areas. The prevalence of hypertension was higher in men (50.5%) that in women (44 %) but females (P<0.001) were more likely to be aware, treated and controlled when compared with males (Figure 1). Of big concern is the very low percentage of hypertension control particularly in men, in whom only 14% of hypertensives have blood pressure values lower that 140/90 mmHg, while in women was 27%.

Similar data has been previously reported in Colombia showing that being male, younger, a rural resident and having a low level of education was associated with significant lower hypertension awareness, treatment and control [3].

In addition to hypertension, the LATAM PURE study observed that other cardiovascular risk factors as alcohol intake, smoking, low physical activity, abdominal obesity, and diabetes also were more frequent in men than in women, situation that are related with the higher incidence of CVD in men compared to women. Interestingly, while CVD was the most common cause of death in men, cancer was the most common cause of death in women [4]. Leading risk factors for CVD in women were hypertension, abdominal obesity, tobacco use, diabetes, and poor diet, while in men were hypertension, tobacco use, abdominal obesity, low grip strength, and low education level. In women, leading risk factors for death were low education level, hypertension, tobacco, abdominal obesity, and diabetes. In men, tobacco use, hypertension, low education level, abdominal obesity and low grip strength were the leading risk factors.

These findings suggest that more than half of CVD cases in both sex in LATAM could be averted by focusing on modifying metabolic risk factors and policies to reduce tobacco use. Also, our results confirm the importance of population level strategies to improve the awareness, treatment, and control of hypertension. Improving hypertension management, particularly in youth male, will require understanding context-specific barriers that limit care and system-level changes directed at overcoming these barriers. Socioeconomic disparities are related to differences in behavior and lifestyle habits such as drinking and smoking. Finally, educational levels and very low income are associated with lower social support and a more limited access to healthcare access, leading to lower detection and treatment of hypertension and associated risk factors. The use of combined therapy could be significantly influenced by income. It is well known that the availability and affordability of medicines impact in the effective BP control. These data highlight the importance of developing appropriate policies aimed at eliminating social and economic disparities, which reduce the access to the management and control of hypertension in LATAM. Therefore, any proposed program to improve the detection, treatment and control of hypertension must include the participation of different actors of society and not only the health system [5].

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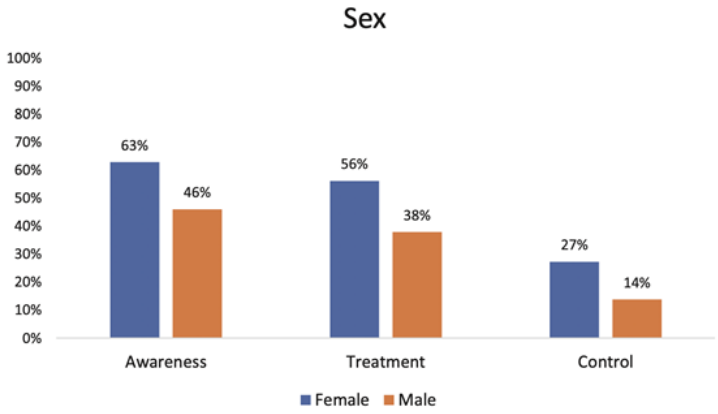

Figure 1. Multivariable adjusted prevalence of awareness, treatment and control of hypertension by sex in Latin American countries. All subgroup P values less than 0.001. Modified of Lamelas P, et al [2].

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LEARNING THE ROPES: ASPECTS ON MALE VS. FEMALE SEX IN HYPERTENSION

Organ damage and pathophysiology

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Pathophysiology

Chronic hypertension leads to structural and functional changes in the heart and arteries.[1] The prevalence of hypertension-mediated organ damage increases with the severity and duration of hypertension. However, the development of organ damage in essential hypertension is influenced by a number of factors beyond the degree of pressure overload, including sex, ethnicity, sympathetic nervous activity, the renin-angiotensin-aldosterone system and co-morbidities (Figure 1).[2] Presence of co-morbidities like obesity and type 2 diabetes mellitus are associated with higher risk of hypertension-mediated organ damage resulting from profound metabolic changes, including disturbed sodium and water handling, paracrine effects of visceral fat tissue, cardiovascular inflammation, and secretion of vascular growth factors.[2] Hypertension is also in itself an inflammatory state.[3] Experimental research has demonstrated that hypertensive stimuli like angiotensin II and high salt intake activate T-cells that become pro-inflammatory and infiltrate the heart, arterial adventitia and periadventitial fat, brain and kidney.[3] These T-cells produce cytokines and interleukins that modulate hypertension and end-organ damage in a sex-specific manner.[4] However, the role of these factors in pathogenesis of organ damage in hypertension needs to be tested in clinical studies.

Cardiac organ damage - more than LVH

Cardiac organ damage is common in hypertension, and may be identified by non-invasive cardiac imaging methods including electrocardiography, echocardiography, cardiac magnetic resonance imaging and cardiac computed tomography of which the former two are particularly recommended for widespread use.[1]

Use of echocardiography may optimize cardiovascular risk assessment and management in many hypertensive patients.[1] Left ventricular (LV) hypertrophy (LVH) is considered the hallmark of hypertensive heart disease and found in 30% of subjects even in mild hypertension, and in up to 90% of subjects with severe hypertension by echocardiography. The prevalence of LVH varies with ethnicity and disproportionally affects black individuals.[5] LVH is also more prevalent and less modifiable by treatment in women than men.[6] LVH profoundly influences prognosis in hypertension, and presence of LVH is associated with nearly a tripled risk of cardiovascular events in hypertensive subjects.[7] LVH also offsets sex-differences in cardiovascular risk, so that women and men have the same risk when LVH is present in hypertension. Several clinical trials have documented that antihypertensive treatment reduces the prevalence of LVH in up to 70% of subjects, particularly by the use of angiotensin II receptor blockers or angiotensin converting enzyme inhibitors. In contrast, studies from clinical practice have demonstrated that LVH regression occurred in a minority, around 14% of subjects. In the Campania Salute Network project, new-onset LVH was detected in 21% of patients during 16 years of follow-up.[8] Women and obese patients were less likely to achieve LV regression, pointing to the multifactorial pathophysiology of hypertensive organ damage.

Beyond LVH, a number of other measures of cardiac organ damage have been well documented as prognosticators in hypertension, including LV systolic

and diastolic dysfunction and left atrial (LA) dilatation. Thus, hypertensive heart disease should no longer be perceived as synonymous with LVH, but rather as an entity including different types of hypertension-mediated cardiac structural and functional changes that are all associated with high risk for clinical cardiovascular disease. Most hypertensive patients with LVH have normal LV systolic function when measured by ejection fraction (EF) at rest. Reduced EF is more commonly found in men than women, and in patients with reduced renal function or concomitant coronary artery disease. However, reduced LV myocardial function is often found in hypertension despite normal EF when assessed by more sensitive measures such as global longitudinal strain or midwall shortening. Presence of reduced systolic or diastolic LV function is associated with reduced prognosis in hypertension.[1,2] It is well demonstrated that women have higher indices of LV systolic function than men both in normotension and in hypertension. Thus, sex-specific cut-off values for identification of cardiac organ damage including LVH and LV systolic dysfunction are recommended by current guidelines.[1]

LA dilatation may reflect chronically reduced LV diastolic function or atrial cardiomyopathy. In hypertension, LA dilatation is more common in women than in men, and predisposes to atrial fibrillation, heart failure and ischemic stroke. In the community based Tromsø Study, uncontrolled systolic blood pressure was associated with a 2-fold increased risk of atrial fibrillation in women, but only a 50% increased risk in men.[9] In middle-aged obese subjects, the majority has a dilated LA. The LA is a thin-walled structure, and antihypertensive treatment does not effectively reduce LA size, pointing to the importance of preventing rather than treating cardiac organ damage.

Arterial damage

Increased arterial wall thickness and stiffness may antecede the onset of hypertension, but is also a common type of organ damage in chronic arterial hypertension. The mechanisms of arterial stiffening involve alteration of extracellular matrix in the arterial wall, smooth muscle cell hypertrophy and endothelial dysfunction that may be linked to aging, sex, obesity, glucose metabolism and genetic factors as well as hypertension. Arterial compliance is physiologically lower in women, while arterial elasticity is higher during the reproductive age, reflecting vascular effects of progesterone and estrogen. Sex differences in arterial inflammation, oxidative stress and major blood pressure regulators also contribute to the observed differences in the arterial function. Arterial stiffness may be assessed by pulse pressure measurement, echocardiography, vascular ultrasound or arterial applanation tonometry.[1] Several clinical studies in hypertension and population-based cohorts have demonstrated that higher arterial stiffness reflected by pulse pressure/stroke volume index or carotid-femoral pulse wave velocity (cf-PWV) predicts increased cardiovascular morbidity and mortality.[1] Women have higher arterial stiffness than men when assessed by pulse pressure/stroke volume index, but lower when assessed by cf-PWV. There is an urgent need for better standardization of diagnosis of increased arterial stiffness in clinical practice, including sex-specific cut-off values for identification. In the Framingham Heart study, increased cf-PWV was found in 60% of controlled and 90% of uncontrolled treated hypertensive subjects, based upon sex-specific mean values for cf-PWV in their cohort.[10] These findings point to the superiority of prevention rather than treatment of arterial organ damage in hypertension.

Conclusion

In conclusion, hypertension-mediated organ damage in the heart and arteries is multifactorial and results from sex-specific interplay between hemodynamic factors, cardiovascular risk factors, co-morbidities and immune activation. Early diagnosis and management of hypertension and other cardiovascular risk factors in the individual subject may prevent development or slow progression of organ damage. Increased understanding of role of the immune system in development of organ damage in clinical hypertension is spoken for.

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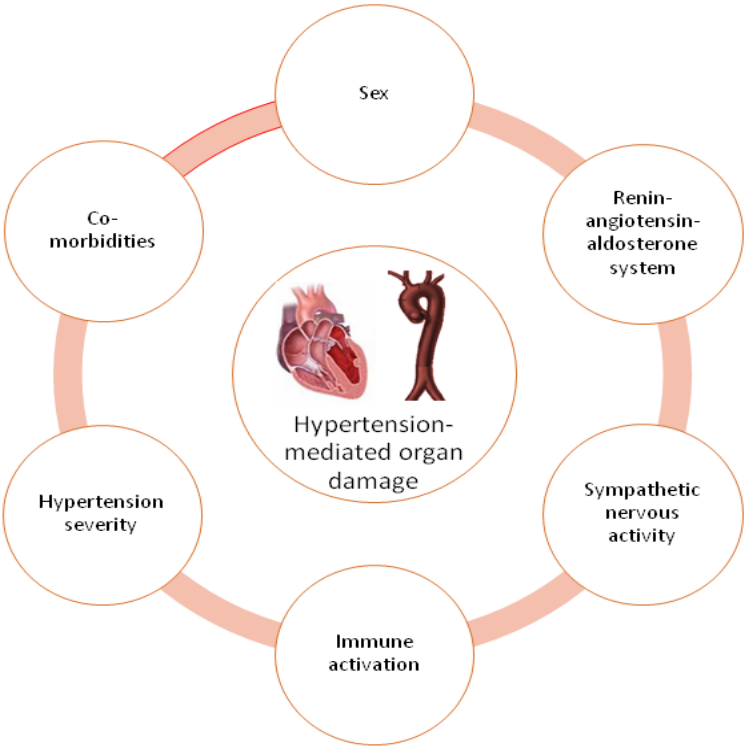

Figure 1. Factors impacting development of hypertension-mediated organ damage in the heart and arteries

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LEARNING THE ROPES: ASPECTS ON MALE VS. FEMALE SEX IN HYPERTENSION

Sex Differences In Antihypertensive Treatment: Where Are We And Where Do We Go From Here?

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Antihypertensive treatment in hypertension guidelines worldwide do not differentiate the management of hypertension by sex except for pregnancy specific recommendations and avoiding RAAS inhibitors in childbearing potential women. However, there are some compelling reasons that suggest a 'one size fits all' approach may miss important considerations when treating non-pregnant women with hypertension. In this article, we will highlight key sex differences in hypertension treatments including surveillance of hypertension to initiate treatment, sex dimorphism of pharmacological response to drug therapies, and evidence to date on effectiveness of antihypertensive treatments in women and men. We will also discuss potential future strategies to reduce treatment gaps.

Hypertension surveillance policies for initiating and intensifying hypertension treatment generally do not account for the varying development and control of hypertension throughout a woman's life span and among higher risk subgroups of women. Earlier in the series, the regional differences in hypertension epidemiology have been well described. In brief, while younger and middle aged men develop hypertension at a higher prevalence than women, this relationship reverses once women reach menopause. Elderly women with hypertension often outnumber men at this stage and exhibit a greater burden of CVD risk than men. Despite this surge in hypertension diagnosis, CVD risk and therefore the need to initiate drug treatment in women, guidelines do not recommend an intensification of monitoring or treatment during these critical periods. Further, women aged greater than 60 years have worse hypertension control of than men at any age. These differences can be amplified by ethnicity and socioeconomic status. In the US, African, Latin and Asian American women had worse control of hypertension than other groups [(1)]. Data from the Bangladesh Demographic and Health Survey (BDHS 2011) of 3870 males and 3955 females, found that non-working women were less likely to be prescribed antihypertensive compared with men (67% vs. non-working males 77%, $p < 0.05$) (2). Women living in poverty had less antihypertensive medication use then men living in poverty [(2)].

In addition to the sex based differences in physiologic mechanisms underlying hypertension described by Drs. Gerdts and Midtbö that could affect therapeutic strategies, there is also gender dimorphism in the pharmacological response to antihypertensive medications. The metabolism and bioavailability of anti-hypertensive drugs depends on sex hormone-regulated absorption for some medications, hepatic cytochrome enzyme metabolism and clearance (3,4). Women have on average lower weights but higher proportions of adipose than men that may result in a lower volume of distribution to hydrophilic medications but a higher volume of distribution to lipophilic treatments [(3,4).] Several studies identified sex differences in activity levels of different hepatic cytochrome P450 enzymes that could have various effects on drug metabolism. CYP 3A4 is involved in the metabolism of about 50% of drugs and women frequently have higher clearance of drugs metabolized by this enzyme [(5)]. Women's eGFR is also 10-25% lower then men indicating lower clearance of antihypertensive treatments.

While the clinical relevance of these pathophysiologic differences and pharmacologic responses to antihypertensive drugs is still unclear, women experience generally increased adverse effects from antihypertensive therapy compared with men. ACE-inhibitor associated dry cough is three times more common in women than men [6]. Women have more diuretic-induced hypokalemia and hyponatremia and less gout than men [6]. Women also report higher rates of peripheral edema with calcium channel blockers than men. Women appear to have more adverse effects with most antihypertensive agents than men except for mineralocorticoid antagonists. Thiazide-type diuretics reduce urinary calcium excretion helping to maintain cortical bone density and lower the risk of osteoporosis in postmenopausal women [7]. This is associated with a reduced risk of hip and pelvic fractures. There are limited sex specific analyses of other adverse effects such as the cancer risk but a recent network meta-analysis found no differences among the antihypertensive drug classes for risk of breast cancer [8].

Antihypertensive treatment significantly reduces cardiovascular disease risk and the ISH Global practice guidelines recommend initiating treatment with ACE inhibitor and calcium channel blocker. However, a meta-analysis of 46 population-based studies from 22 countries, of 123,143 men and 164,858 women aged less than 60 years found that women were more likely prescribed diuretics, while men more often prescribed ACE-inhibitors and calcium–antagonists [9]. Although these differences have been attributed to the avoidance of RAAS blockers in women of childbearing age, an observational study from Sweden found these sex differences persisted after adjustment for factors influencing the choice of these medications including age [10]. Further, several reports raise concern that adherence to medications being may be worse in women than men. In an observational study of 60 526 patients aged 40–80 years newly treated with antihypertensive drugs in the Italian Lombardy Region, women had a 10% higher discontinuation rate compared with men within the first year of their prescription [11]. Although based on self-reported data, which has a higher risk of bias, a recent systematic review of patients aged 65 years or older, found that women had lower self-reported adherence than men [12]. Whether these cumulative differences in women in prescribing and non-adherence, especially older women, contribute to the worse control of hypertension or higher CVD risk in elderly women is unclear.

Clinical trial inclusion of women has been historically poor, and largely focused on Western populations, hindering our ability to understand sex differences of antihypertensive treatments on blood pressure lowering or effectiveness on reducing CV endpoints. A systematic review of 598 CVD trials found that enrollment of women was low at 21% between 1986 and 1990 [13]. This increased to 33% between 2011 and 2015, yet still remained below the expected prevalence of hypertension in women in the population and below the threshold to detect meaningful differences in CVD endpoints in trials. An overview analyses by Turnbull and colleagues from 2008 of 31 large randomized trials of 103,268 men and 87,349 women, found the degree of BP reductions achieved during these studies was generally similar for each antihypertensive comparison between men and women [14]. Further, there were no significant sex differences in reduction of major CV events from degree of BP lowering or effect of angiotensin-converting-enzyme inhibitors, calcium antagonists, angiotensin receptor blockers, or diuretics/beta blocker based treatments [15]. In more recent clinical trials (see Table 1) including SPRINT that enrolled 36% women, there were no significant differences in the main CVD endpoint in the women and men subgroups [16]. Likewise, the ACCOMPLISH trial published in 2008 enrolled 11506 patients (39.5% women) compared ACE inhibitor and calcium channel blocker with hydrochlorothiazide and beta blocker also reported no interactions by sex on fatal and non-fatal CV endpoints [17]. A pre-specified subgroup analysis of the VALUE trial, comparing valsartan to amlodipine in 15 245 (42% women) showed higher cardiovascular morbidity/mortality with valsartan than amlodipine in women, but not in men [18]. HOPE 3 was a 2-by-2 factorial trial that randomly assigned 12,705 participants (46% women) at intermediate risk who did not have cardiovascular disease to candesartan plus hydrochlorothiazide vs. placebo [19]. There were no significant sex differences in the composite risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke after a median follow-up was 5.6 years (p for interaction 0.32). Taken collectively, these studies suggest that there is no evidence for significant sex based differences in the effect of antihypertensive therapies in those with hypertension. However, our understanding of the effects in important women subgroups such as post menopausal women or women of differing ethnicity remain largely unknown.

There is a paucity of sex specific data to guide hypertension treatment in non-pregnant women despite the fact that almost 800 million women worldwide are

estimated to have hypertension. Where do we go from here? Multipronged strategies are needed to close our knowledge gaps to optimize treatment in diverse women globally.

1. More inclusion of women and reporting sex specific data in CVD treatment trials including women of differing ethnic groups and regions to identify optimal treatments across diverse groups of women.

2. Systematic review of existing studies to evaluate the effects of antihypertensive therapy on CV and other endpoints in subgroups of women by region/ethnicity and age compared with men.

3. Investigate personalized models of care targeting women with more frequent hypertension monitoring, initiation of therapy and tracking adherence during key periods across a woman's life span including the peri- and post-menopausal period.

4. Continue to prescribe antihypertensive therapy as per guidelines as there is no evidence to date that there are clinically relevant sex differences with these treatments.

5. Aggressively monitor for and manage adverse effects from medications in women.

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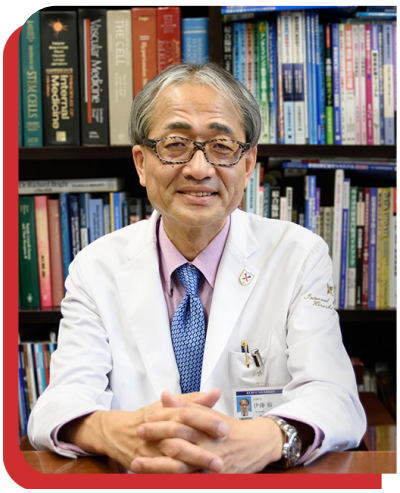
INVITED PAPER

The ISH Meeting: A new normal born in Kyoto!



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ISH2022 will be held from October 12 to 16 2022 in the City of Kyoto at Kyoto International Conference Center (ICCK) with the theme of "The Wisdom for Conquering Hypertension."

COVID-19 has deprived us of gathering opportunities for quite some time, and we really miss the liberty to meet, chat and have fun with many of our friends and colleagues from all over the world. We believe face-to-face meetings bring us more active debates and create stronger ties than any other formats, and we expect the COVID-19 pandemic will be over by October 2022. However, even if this is not the case, we will take all possible measures to hold a face-to-face meeting ensuring your safety.

Aiming at conquering Hypertension, ISH2022 also aims at creating a new scope of health and longevity by focusing on the three pillars: "Food (food and nutrition)", "Move (movement and fitness)", and "AI (artificial intelligence and digital technology)."

By bringing together multidisciplinary wisdoms regarding hypertension-related diseases, we aspire to explore new directions in diagnostics, prevention and treatment, as well as generate a new paradigm in our shared mission to control the disease.

It is with pride that we invite all of you to participate in the ISH2022. We strongly believe that you will find Japanese hospitality extremely satisfying and will be able to deepen and widen your knowledge and expertise to learn from the best.

Program updates

Our scientific program committee members are intensively working to make the ISH2022 informative, impressive and fruitful to our friends and colleagues, by inviting knowledge and intelligence from all over the world, and Professor Shinya Yamanaka, 2012 Nobel laureate has already confirmed his commitment to the ISH2022 in October 2022:

We will update program information on our website, so don't miss the latest information!

Counting down to the ISH2022!

We have supporters from all over the world to promote ISH2022, and they will serve as ambassadors in their regions. From 1 year before the ISH2022 starts, we will start counting down with the video message from ambassadors and supporters of the regions. We will be counting down and letting the excitement build for the ISH2022. You will find the videos on the official website and social media.

Please visit our website, Facebook, twitter and Instagram to find out the latest information and keep yourself in the loop of communication!

Shinya Yamanaka, The discoverer of iPS cells, 2012 Nobel Prize laureate

Director, Center for iPS Cell Research and Application (CiRA), Kyoto University.

Kyoto is a must-see destination to get a glimpse of all of Japan having a higher concentration of cultures in the entire country. Kyoto has 17 UNESCO World Cultural Heritage Sites, and is brimming with unique culture and atmosphere.

The city of Kyoto offers you opportunities to gain meaningful hands-on experience of rich Kyoto culture through Tea Ceremony, sake brewing, kimono wearing, swordsmanship, and more. Moreover, Japan is renowned for its safety and the compactness of Kyoto makes for wonderful strolling during free time. You will experience unique Japanese culture when you explore the city of Kyoto during your stay.

We have about 1 year to go for the ISH2022, and we appreciate your attention and cooperation for the successful gathering. We look forward to sharing an excellent time in this beautiful city of Kyoto.

Kinkakuji Golden Pavilion, One of the 17 World Heritage Site in Kyoto first built in 1397

Kiyomizudera Temple, One of the 17 World Heritage Site with over 1,200 years of history

Fushimi Inari Shrine, Famous for its thousands of torii gates, It is known as one of the country's top tourist destinations

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INVITED PAPER

The Japanese Perspective on the Global Burden of Hypertension Cardiovascular Disease

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Recently the International Society of Hypertension (ISH) has conducted the May Measurement Month (MMM) for the global campaign to raise awareness of the need for people to get their blood pressure checked.[1] Of the more than 1.5 million people, 32.0% had never had a blood pressure (BP) measurement before, and 34.0% had hypertension, of whom 31.7% were controlled to <140/90 mm Hg, and 23.3% of participants had untreated or inadequately treated hypertension. In addition, NCD Risk Factor Collaboration reported that people aged 30–79 years with hypertension doubled from 1990 to 2019, from 331 to 626 million women and 317 to 652 million men in 1990 to 2019, respectively.[2] However, in high-income countries consisting of western and Asian-Pacific, including Japan, hypertension has declined. According to the National Health and Nutrition Survey in Japan, for more than half a century, the average systolic BP of Japanese people aged 60 and over has dropped by 30 mmHg to the 130 mmHg level, but it is still high BP category (Figure 1). Although blood pressure has dropped, the rate of high blood pressure in the elderly is still high.

Table 1 shows the blood pressure categories of the major hypertension guidelines. The high-normal BP of Japanese Hypertension Guidelines is a unique category compared to other countries' categories.

The Circulatory Risk in Communities Study showed that the population attributable fractions of stroke and coronary artery disease were the largest for hypertension (46% and 29%).[3]

The Chronic Kidney Disease-Japan Cohort (CKD-JAC) study showed that the risk of cardiovascular events increased as the eGFR decreased, with a 3.16-times higher in CKD stage G5 (eGFR<15 ml/min/1.73 m2) than that in CKD stage G3a (eGFR=45–59 ml/min/1.73 m2). Thus, the risk of CVD and all-cause death was related to the decrease in eGFR but not necessarily elevated in proportion to the progression of the CKD stage in Japanese patients with predialysis CKD under a nephrologist's care.[4] The CKD-JAC study also showed that elevated SBP and increased urinary albumin-to-creatinine ratio were 1.2- and 4.5-times increased risks of CKD progression to end-stage renal disease in Japanese patients under nephrology care. [5] Middle-aged healthy Japanese men without hypertension at the baseline (n=3172) were observed 474 participants developed hypertension during a 9-year study period. The generalized estimating equation analysis revealed that both radial augmentation index (estimate=0.06, SE=0.03, P=0.05) and brachial–ankle pulse wave velocity (estimate=0.007, SE=0.002, P<0.01) showed significant longitudinal association with new onset of hypertension, with no significant interaction. [6]

During an average of 7.8 years of follow-up, 720 participants experienced the primary outcome. The adjusted hazard ratios (HRs) of combined CVD and all-cause mortality significantly 1.37-, 1.6-, and 2.42-times increased with ABI=0.91-0.99, ≤0.90, and(≥1.30, compared with ABI =1.10~1.19. Adding ABI to a model with the Framingham risk score marginally improved the c-statistics (p=0.08). [7]

The present study suggests that lower and higher ABI are significantly associated with an increased risk of CVD and all-cause mortality in the Japanese population. The ABI, which is easily measured by oscillometry, may be incorporated into daily clinical practice to identify high-risk populations.

The NIPPON DATA80 demonstrated that young-to-middle-aged participants aged 30–49 years (mean age, 39 years) with isolated systolic hypertension had a higher risk of CVD mortality, including CHD and stroke, than those with normal BP after adjustment for demographics and other CVD risk factors.[9]

One of the oldest and well-designed cohort studies, the Hisayama Study, conducted a genome-wide polygenic risk score, which was a significant risk factor for ischemic stroke independent of environmental risk factors. This finding suggests that a polygenic risk score may be helpful to identify individuals at a high risk of ischemic stroke. Subjects with the highest quintile level of a genome-wide polygenic risk score had a 2.44-fold greater risk for ischemic stroke than those with the lowest quintile level.[10]

A risk score for hypertension was developed in the Hisayama study (C statistic was 0.812, 95% CI, 0.791–0.834), where the risk prediction model for hypertension consisted of age, sex, SBP, DBP, use of glucose-lowering agents, BMI, parental history of hypertension, moderate-to-high alcohol intake, and the interaction between age and BMI.[11]

The Suita study, a Japanese urban cohort study, published a series of classical risks and developed risk scores for ischemic heart disease, atrial fibrillation, and cardiovascular disease. Ahmed (right side of the photo) is currently developing a stroke risk score model, and Haytham (left side of the photo) is developing a hypertension risk score model. We are all studying and researching cardiovascular diseases such as hypertension.

Table 1. Blood pressure categories of the world's major guidelines

ISH 2020		JSH2019		ESC/ESH 2018		ACC/AHA 2017	
Category	BP levels, mmHg	Category	BP levels, mmHg	Category	BP levels, mmHg	Category	BP levels, mmHg
		Normal BP	<120/80	Optimal BP	<120/80	Normal	<120/80
Normal BP	<130/85	High-normal BP	120-129/<80	Normal BP	120-129/80-84	Elevated	120-129/<80
High-normal BP	130-139/85-89	Elevated BP	130-139/80-89	High-normal BP	130-139/85-89		
Grade 1 HT	140-159/90-99	Grade I HT	140-159/90-99	Grade I HT	140-159/90-99	Stage 1	130-139/80-89
Grade 2 HT	≥160/100	Grade II HT	160-179/100-109	Grade 2 HT	160-179/100-109	Stage 2	≥140/90
		Grade III HT	≥180/110	Grade 3 HT	≥180/110		

BP, blood pressure; HT, hypertension.

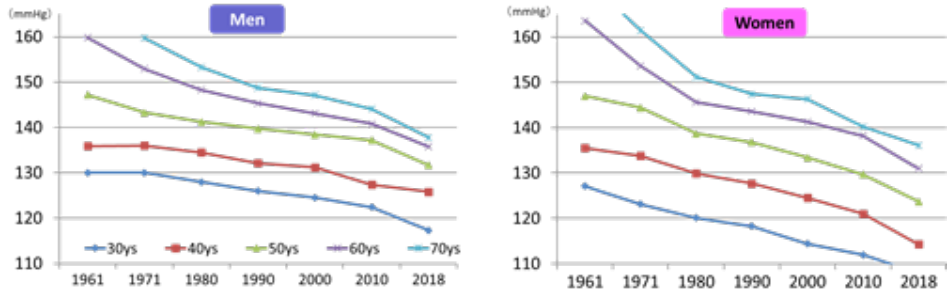

Figure 1. Changes in average systolic blood pressure by gender and ages more than half a century

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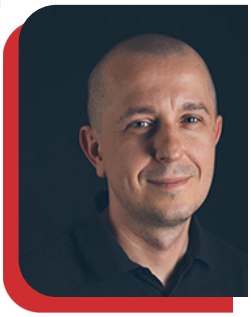
JOURNAL OF HYPERTENSION

The future of the Journal of Hypertension

Maciej Tomaszewski[1] and Philip J. Daly[2]

[1]ISH President and Chair, Board of Management

[2]Lead Publisher, Wolters Kluwer Health



Wolters Kluwer Health, the European Society of Hypertension, and the International Society of Hypertension were pleased to announce Professor Tony Heagerty as the new Editor-in-Chief of the Journal of Hypertension earlier this year. Tony was chosen from a group of high calibre applicants by the Board of Management, chaired by Professor Fadi Charchar. Tony Heagerty is Head of the School of Medical Sciences at the University of Manchester, UK, and is a previous President of the ESH and ISH, and the British and Irish Hypertension Society.

We thank his predecessor Professor Giuseppe Mancia, and his Editorial Team, for the many years' service and commitment to the Journal, and their support previously given to Professor Alberto Zanchetti, and now to Tony as he embarks on his Editorship. During the transition period Giuseppe is supporting Tony as Consulting Editor. Special mention goes to the Editorial Office staff in Milan who have set a high bar of service to emulate - Lidia Rossi, Paulina Wijnmaalen, and Marilisa Rossi. Lidia and Paulina, with the much-missed Cinzia Tiberi in prior years, have been central in the day-to-day communication with the Publisher.

Tony is keen to continue the development of the Journal and exploring ways of communicating in ways other than through the Journal's pages. He has already appointed a Web Editor who will develop social media presence and outreach to a wider audience through the Journal webpages. We acknowledge that the change in Editorship begins a new chapter for the Journal, and we wish Tony and his Team well in their endeavours.

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JOURNAL OF HYPERTENSION

The new editor's visions

TONY HEAGERTY

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I began my academic career under the supervision of Professor John Swales in Leicester and at that time he became the first Editor in Chief of the Journal of Hypertension so I have always had a deep affection for it. John was an outstanding clinician and supported his junior lecturers with late night suggestions for new experiments and regular examination of our data as they emerged. In his laboratory I performed the small artery studies in hypertensive patients with Christian Aalkjaer that led to my being awarded the ISH Prize for an Outstanding Young Investigator in 1988 and my British Heart Foundation Senior Research Fellowship. I delivered the Royal College of Physicians Goulstonian Lecture as the youngest elected Fellow in 1990 and was appointed Professor of Medicine in Manchester in 1991where we have established a Tertiary Hypertension Service as well as a Cardiovascular Research Centre. I gave the Bjorn Folkow Lecture in 2006 and was awarded the Robert Tigerstedt Lifetime Achievement Award by the ISH in 2016. I have served as President of the ISH, ESH and the British and Irish Hypertension Society. Hypertension is in my academic DNA.

Since 1 July 2021, I have had the honour of taking over as Editor in Chief of The Journal of Hypertension and in doing so fulfilled an ambition inspired by John Swales. This has been no easy task: The Journal has been managed with exemplary skill by Professor Giuseppe Mancia and his team and has grown in celebrity and stature immensely under his leadership. We owe him a deep debt of gratitude and I have large shoes to fill. I have formed an Executive Team and selected academic colleagues from my own institution as well as the United States, Europe and Africa with an accent on a change in sex balance and ethnicity. We are excited by the prospect of reaching out and publishing work from all regions of the world. The team comprises Professor Jane Reusch (Denver, Colorado,USA), Dr. Brandi Wynne (Salt Lake City,Utah,USA), Dr. Jana Brguljan-Hitij (Ljubljana, Slovenia), Dr. Adam Greenstein (Manchester, UK), Dr. Sophie Saxton (Manchester, UK) and Professor Augustine Odili (Abuja, Nigeria). Within it is the skill set to cover Hypertension in all its aspects and also the broader remit of Women's Cardiovascular Health and Diabetes. They together, with an expanded Editorial Board, will reflect our global commitment and enhanced inclusivity. Already we have invited additional members to help us. Our Editorial Office will be run in Manchester by Mrs Julie Heydon. The Journal will be promoted on Media Platforms by Dr. Sarah Withers (Salford, UK). We shall be using podcasts with our authors to promote their work, introducing distillations of papers for patients and tweeting hard and will reach out to non-scientists as well as our research community. It is a vast family! We will be looking to provide Position Statements on areas of Practice Controversy for Clinicians as well as examining cardiovascular disease and its management in different regions around the world together with a commitment to continue to publish the very best papers after rigorous peer review.

From left to right: Tony Heagerty, Jane Reusch, Sophie Saxton, Brandi Wynne, Augustine Odili, Sarah Withers, Adam Greenstein, Jana Brguljan and Julie Heydon

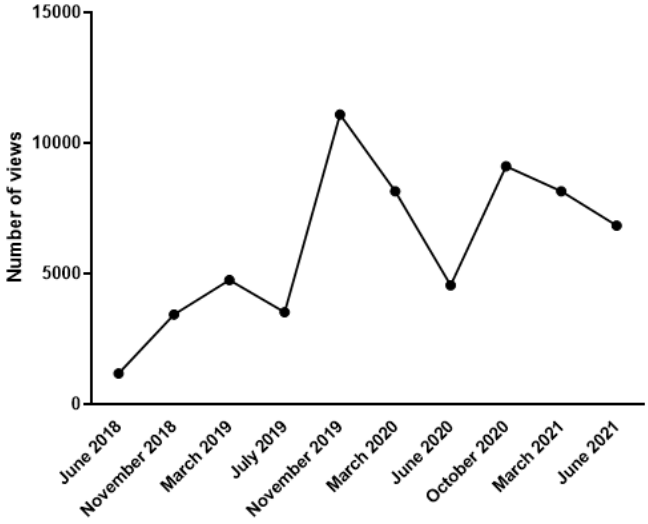
Tony Heagerty - tony.heagerty@manchester.ac.uk

"DDD" DYLAN'S DISTRIBUTION DATA

DYLAN BURGER

Ottawa Hospital Research Institute,
Ottawa, Canada.

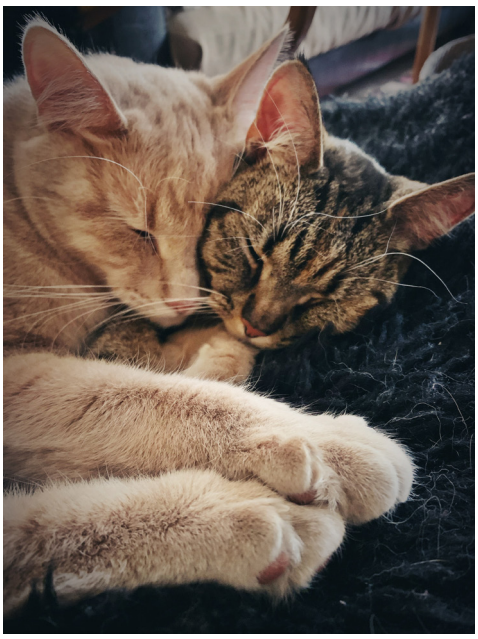
The June edition of Hypertension News was viewed by approximately 7000 people. This was down slightly from our two most recent issues but this number should be taken in context. The summer issue of Hypertension News has historically been viewed by fewer individuals, likely owing to the holiday season for many of our readers. In fact, when compared the summer issues from 2019 and 2020 this issue showed about a 50% increase in readership. The issue had focused heavily on the 2021 scientific meeting and this content drew considerable attention. The feature on 2021 Franz Volhard Award Winner Ernesto Schiffrin was heavily read as were the "hot off" features from Cesar Romero (Salt and hypertension) and Nicolas Renna (COVID19 and hypertension: Are we facing a syndemic?) The Hypertension News editorial board is grateful for the support and interest of our loyal readers.



Dylan Burger - dburger@uottawa.ca

MEANWHILE IN 'HYPERTENSION MEWS'...

all is well and cosy now when more
than half of the adult Swedes have
been Covid-19- vaccinated



NEW BLOOD

Introduction

CHARLOTTE MILLS

Hugh Sinclair Unit of Human Nutrition, University of Reading, UK

DOI:10.30824/2110-13

In this issue of Hypertension News we continue to publish interesting short papers by future leaders on timely topics spanning clinical and basic science.

First we have Nicolas Renna from UNCuyo-CONICET, Argentina who presents an article on adherence to hypertensive treatment. He discusses the importance of detection of non-adherence and presents medication event monitoring system (MEMS) as a useful tool for monitoring medication use. He concludes by discussing potential options to minimise non—adherence, such as single pill combination.

Moving to the Federal University of ABC, Brazil, Carolina Victoria Cruz Junho and Marcela Sorelli Carneiro-Ramos' paper describes the kidney-heart axis in relation to the immune system. They describe their work on acute kidney injury in an ischemia reperfusion model, detailing how this induces acute inflammation and cardiac hypertrophy as well as electrical changes. They go on to detail their findings linking specific cytokines to acute kidney injury-induced cardiac arrythmia.

Lastly, an article on the emerging field linking the gut microbiota and hypertension. Rikeish R. Muralitharan, Monash University, Australia explains the complexity of gut microbiome research due to the impact of intrinsic and extrinsic factors. He argues the benefits of investigating functionality of microbes and presents the discovery of the absence of butyrate producing bacteria in hypertensive patients as an example. Rikeish presents potential approaches to further advance the field and highlights the need of research to focus on causal links between the gut microbiome and hypertension.

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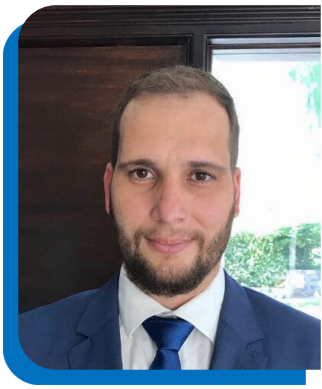
NEW BLOOD

Adherence to Antihypertensive Treatment and Associated Factors



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DOI:10.30824/2110-14

High blood pressure is one of the most important risk factors for ischemic heart disease, stroke, chronic kidney disease, and dementia. The prevalence of hypertension has decreased substantially in high-income regions. In contrast, blood pressure has risen in low- and middle-income countries. The use and efficacy of hypertension treatment vary substantially between countries. Factors influencing this variance include a country's financial resources, the extent of health insurance and health infrastructure, the frequency with which people interact with doctors and non-medical health personnel, and the availability of medicines. [1]

One of the fundamental pillars to achieve adequate blood pressure control is adherence. Adherence to hypertension treatment 1 year after onset is near to 50%. [2,3]. The adherence was defined as the extent to which a person's behaviour when taking medications, following a diet, and making lifestyle changes is consistent with the agreed-upon recommendations of a healthcare provider. [4]

Adherence is a process characterized by 3 components: initiation, implementation, and discontinuation. In clinical practice, non-initiation reaches reach to > 20% in hypertension treated patients; however, this phenomenon can vary considerably according to the countries and access to medications. When the next dose is omitted to be taken and then treatment is stopped, this marks the interruption of the treatment. This parameter allows the definition of persistence, which is the period between the start and the last dose immediately before to interruption. Non-persistence is one of the most frequent causes of poor adherence in hypertension, with 50% of patients having interrupted treatment one year after starting treatment. [5]

But how can we detect non-adherence to antihypertensive treatment? The ideal method for assessing drug adherence should provide reliable capture, storage, analysis, and communication of dosing history data in a way that makes it difficult or impossible for patients or trial staff to censor or manipulate the data. To date, none of the available systems meets all these criteria.

A method that has gradually been acquiring more evidence, the electronic monitoring system for medication adherence, known as the Medication Event Monitoring System (MEMS), but its implementation in clinical practice is still limited to expert centres. This system is analogous to the determination of drug levels where the total absence of a compound is more relevant in terms of non-adherence than the actual presence of the drug (97% accurate). Besides, electronic monitoring systems provide information on drug use behaviours (taking, time, frequency of omissions, compensatory intakes) based on dosing history. [6]

The selection of prescribed drugs to antihypertensive treatment has an impact on adherence and persistence essentially due to the side effect profile, the number of drugs taken and patient confidence. A fixed dose combination that includes two or more active pharmaceuticals combined in a single pill combination (SPC) could be a strategy for overcoming no adherence. The initial choice of antihypertensive drugs it is very important because could affect the patient's first therapeutic experience and the doctor's decisions in daily practice. [7]

SPC is an appropriate therapeutic option and can be implemented in most low-income countries because it is a cost-effective strategy. It also produces a rapid and sustained decrease in BP, since hypertension is a multifactorial disease, the combination of drug classes increases the antihypertensive effect, improving the control rate, also conferring greater cardiovascular prevention. A similar concept is the polypill, which provides this, in addition to adequate blood pressure control, cardiovascular protection because it combines

antihypertensive, lipid-lowering and, although not always, aspirin. [8]

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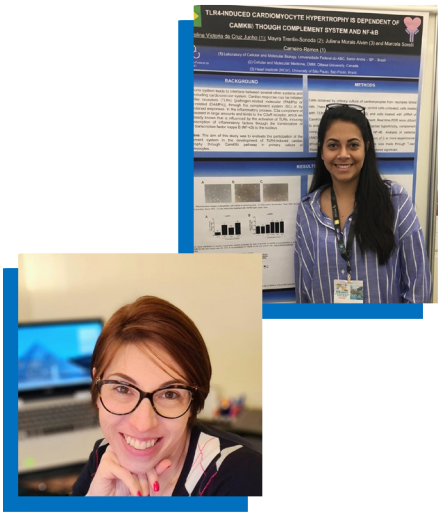
NEW BLOOD

Cardiorenal Syndrome: immune system as an intriguing connector between Heart and Kidney



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DOI:10.30824/2110-15

Since 1836 when Robert Bright first described the relationship between heart and kidneys, the scientific community has dedicated itself to better understanding the mechanisms involved in the kidney–heart axis, known in recent decades as cardiorenal syndrome (CRS) [1]. CRS can be classified into 5 different types, where types 1 and 2 are defined by acute or chronic cardiac alterations that lead to renal dysfunction, types 3 and 4 defined by acute or chronic renal alterations responsible for later cardiac alterations, and finally type 5, characterized by concomitant dysfunctions of the kidneys and heart due to systemic alterations such as

sepsis or diabetes [2]. CRS type 3 affects a large amount of the population and is defined by an acute renal alteration capable of generating important cardiac alterations [3]. The acute kidney injury (AKI) increases from 5% to 30-50% in all patients hospitalized in intensive care units and is present in ~43% of all deaths related to cardiovascular diseases [4]. Ischemia and reperfusion (IR) injury is the main cause of AKI. This is a temporary condition that obstructs the blood flow in the kidney, leading to the release of oxidative stress compounds as well as inflammatory cytokines [5]. In this sense, our laboratory has been seeking to understand the cellular, molecular and functional mechanisms involved in cardiac alterations induced by AKI in an IR model in mice.

The AKI induced by the IR model leads to an inflammatory process that seems to be important to the development of heart dysfunction. One of the main focuses of our group was to evaluate the role of innate immunity, represented by Toll-Like receptors (TLRs), in cardiac

tropism modulated by acute kidney injury. First, we demonstrate that IR model are able to induce an acute systemic inflammation (until 8 days of reperfusion) followed by a concentric cardiac hypertrophy (after 15 days of reperfusion) not accompanied by fibrosis. Besides, TLRs 2 and 4 are essential for cardiac hypertrophy development observed in IR model [6]. In addition to cardiac hypertrophy and acute inflammation, it was possible to observe important electrical changes demonstrated to an increase on action potential duration (APD) and QTc interval [7].

The increased number of pro-arrhythmogenic events stimulated us to investigate the role of some inflammatory cytokines that were shown to be altered in this experimental model. Thus, we studied the role of NLRP3 inflammasome and IL-1b on arrhythmogenic events and we demonstrated, for the first time, that the inflammatory cytokine IL-1b plays a crucial role in cardiac arrhythmia induced by acute kidney injury once knockout models and pharmacological interventions were able to prevent arrhythmogenic events [7]. Besides, other studies by our group have shown that the Renin-Angiotensin-Aldosterone System (RAAS) and the Sympathetic Nervous System (SNS) are important mediators of the kidney-heart axis since cardiac inflammatory events induced by renal IR, caused by the simultaneous upregulation of the SNS and RAAS in the heart, possibly support the mechanism involved in the development of cardiorenal syndrome [8]. Furthermore, it was possible to demonstrate that the IR model mimicking CRS3 presents a specific tissue and time regulation regarding the redox balance, which suggests possible forms of therapeutic interventions [9].

Although some of the mediators of the conversation between kidneys and heart are known, much remains to be explored regarding the mechanisms involved in each type of CRS. Some of them we are currently studying as the participation of mitochondria dysfunction, modulation of lymphocytes and macrophages populations, accumulation of uremic toxins and extracellular vesicles content.

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NEW BLOOD

Moving from Association to Causation: Deciphering the Role of the Gut Microbiota in Hypertension

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DOI:10.30824/2110-16

The gut harbours trillions of microbes including bacteria, fungi, and viruses, collectively known as the gut microbiota. These microbes interact among themselves, but also with the host's immune system and environment (e.g. food). There is increasing evidence to support the role of the gut microbiota and its genome, the gut microbiome, in hypertension[1]. Despite the increasing number of microbe-wide association studies (MWAS), identifying specific causal microbes that contribute to blood pressure (BP) regulation has been challenging[2,3]. This is unsurprising given our experience with genome-wide association studies (GWAS), which have identified hundreds of genes with little understanding about their role in BP control per se[4]. Considering the gut microbiota is influenced by many intrinsic (e.g., host's genetics[5]) and extrinsic factors (e.g. diet, geography, ethnicity, seasonal variations, circadian cycle, and medication use), gut microbiome studies require careful experimental design. This is easier done using laboratory animals than humans[6].

Instead of identifying causal microbes, a more fruitful approach is to assign functions to microbes to better understand their roles. Through this approach, it was shown some bacteria, such as butyrate-producers, are lacking in hypertensive patients. Indeed, we recently discovered that microbial gene pathways might be more important than specific microbial taxa[7]. This has also led to the discovery of the importance of metabolites such as short-chain fatty acids (SCFAs) in hypertension[8] and trimethyl-amine oxide (TMAO) in cardiovascular diseases[9].

To further advance the field, mechanistically linking microbes or metabolites to function and phenotype is essential. There are multiple ways to achieve this, namely a) reverse microbiome approaches, b) forward microbiome approaches, and c) microbe-phenotype triangulation (Figure 1)[9].

An example of the use of these approaches is a recent publication in Circulation Research, by Dr. David Durgan and his team. They elegantly employed some of these approaches to demonstrate mechanistically how the gut microbiota changes with intermittent fasting and how that influences BP[10]. Using a forward microbiome approach, they first compared the gut microbiome between their experimental groups and identified differentially abundant bacteria that metabolised bile acid. To confirm this, they performed caecal and plasma metabolomics and found evidence supporting differences in bile acid metabolites. Armed with sufficient evidence, they went on to use a reverse microbiome approach to confirm their findings by dietary supplementation and agonist treatment. By using a combination of these methods, they were able to pinpoint that increased BP in hypertensive rats was a result of reduced plasma bile acid levels which could be restored with either a) intermittent fasting, b) supplementing cholic acid (precursor of bile acids) or c) agonist treatment of TGR5, a bile acid receptor. Although their studies were not validated in the context of human hypertension, a recent clinical study showed fasting influenced the gut microbiome and reduced BP in patients with metabolic syndrome[11]. However, altered bile acid metabolism was not discovered in those patients, potentially because of differences in the models and diet.

Moving forward, a push towards identifying causal links of the gut microbiome in hypertension is necessary to advance the field. Confirmatory experiments need to be performed and validated in other models and ideally in clinical interventional studies.

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COMMITTEE REPORT

The ISH Corporate Liaison Committee – full speed ahead!

THOMAS UNGER

CARIM- Maastricht University, NL

In the good old days, big pharma would queue up to become a partner of hypertension societies. In those bygone times they all competed heavily to bring new antihypertensives into the clinic and on to the market. There were plenty of new compounds, reflecting an unprecedented drug development in the field of hypertension which had begun in the fifties of the last century. Each decade produced a new class of antihypertensive drugs, their indication crossed the borders of hypertension into heart- and kidney failure and metabolic diseases. As from the early eighties, the inhibitors of the renin-angiotensin system (RAS), first the ACE-inhibitors, then the angiotensin AT1 Receptors blockers (ARBs), started their triumphal march which was crowned by the indication "high cardiovascular risk" by US-American and European agencies for some of their drugs.

In those days, drug companies developing antihypertensive agents were highly interested in partnerships with scientific hypertension-related societies, and this was in many cases a win-win situation. I remember the ISH congress in Berlin, Germany, in 2008, for which I chaired the organizing committee: The sponsorship from pharmaceutical companies, all corporate members of ISH, allowed us to host more than 9.000 participants, and our industrial partners brought many of these delegates from countries all over the world. In return, academic experts from scientific hypertension societies helped these companies to find new targets and develop new blood pressure lowering drugs.

But, as it usually happens, "After the climax comes the fall". The great success of the new antihypertensive drugs, which – alone or in combination - were able to control blood pressure in the vast majority of hypertensive individuals, became their dilemma. Drug patents were gradually expiring, and the development of new cardiovascular agents, notably antihypertensives, became increasingly difficult, due to new administrative and other hurdles, and risky because the broad paths had already been taken and new targets suitable for drug development were scarce. The pharmaceutical companies, one after the other, abandoned the field of hypertension and turned towards other indications such as atrial fibrillation or diabetes mellitus. Or they left the cardio-metabolic field altogether to concentrate on cancer drugs or compounds interfering with the immune system. Consequently, most companies lost interest in long-standing, established partnerships with hypertension societies, and the number of their corporate members dwindled.

In October 2020, I was appointed chair of the ISH Corporate Liaison Committee. My commitment for the ISH has been long-standing: It began already in 1986 as a member of the organizing committee of the ISH congress in Heidelberg, then I chaired that committee both for the ISH congress in Berlin in 2008 and the one in Beijing in 2018. Due to my profession as a clinical pharmacologist, I have had ample opportunities to cooperate with several pharmaceutical companies involved in the development of cardiovascular drugs, and this was probably the reason why I was entrusted with this office. The other distinguished members of the new committee are Fadi Charchar, Rafael Castillo, Adam Greenstein, Dagmara Herring, Markus Schlaich, and Xin Wang.

A year ago, ISH had five Corporate members: three pharmaceutical companies (Abbott, Otsuka, Servier) and two device companies (Medtronic and Omron). Our predecessors, under the leadership of Markus Schlaich, had made great efforts to increase the number of Corporate members, but had unfortunately encountered great difficulties.

One fact which had become quite clear during the last years was that the search for new corporate members should not be confined to the pharmaceutical industry, but had to be extended to companies working in other fields related to hypertension, for instance those with a focus on diagnostics or devices.

For a year, the new committee has met several times via Zoom, and we have encouraged each other to address all industrial contacts already present and to be resilient in case the first responses were negative. The previous committee had produced a useful brochure listing all the mutual benefits of corporate membership. They had also established free advertisements in "Hypertension News": one page for platinum members, half a page for gold members and a quarter page for silver members, together with links to scientific literature which the respective corporate member would like to be considered. Since Hypertension News is downloaded by up 10,000 readers, this offer was thought to be quite attractive, an assumption which turned out to be true in our contacts with future sponsors.

We contacted the companies which had sponsored the recent ESH/ISH/BISH congress in Glasgow along with many others to which members of the committee had established some form of relationship. Many companies were not interested, (which was sadly to be expected), but in the end, we also encountered some willingness for partnership. Up to now, we are happy and proud to have recruited three new corporate members, one platinum, one gold and one silver.

As first new corporate member we could welcome an Austrian company named ATTOQUANT Diagnostics. This relatively young company has successfully tackled an analytical problem which had hampered peptide research for quite a while. They have developed an analytical method to simultaneously detect and quantify peptide hormone cascades "with a major focus on the Renin- Angiotensin-Aldosterone System". Thus, one application of this new analytical method is to identify individual patterns of angiotensin metabolites, for instance after treatment with an ACE inhibitor or an ARB. In addition, they offer highly sensitive analyses of proteolytic enzymes.

The second new corporate member recruited was MERCK Kg aA based in Darmstadt, Germany. This globally acting pharmaceutical company (not to be confused with the US-based company Merck Sharp and Dohme) with its more than 50.000 employees looks back to a long history of drug development within the cardiovascular, endocrinological and other fields. In the high times of digitalis therapy, many doctors were familiar with a drug called Digimerck (Digitoxin). Merck Kg aA is the first pharmaceutical company which came back to ISH as a corporate, and we very glad about their engagement, hoping that others will follow.

Finally, we could recently welcome a third new corporate member: A Swiss-based start-up company called AKTIIA founded in 2018. This company develops and produces novel devices for cuffless optical blood pressure monitoring. They have already established a relationship with prominent experts within our society. In February 2021 Aktiia proudly announced 1 million blood pressure readings with their devices.

Hence, within a year, the new ISH Corporate liaison committee has been able to recruit three new corporate members, but off course, we strive for more! As we all know, hypertension is a condition with close links to cardiometabolic and renal diseases. In many cases, new drugs against these diseases also have an impact on high blood pressure. Hence, today, a hypertension society like ISH has to go "beyond blood pressure" stretching out to what we call comorbidities and their treatment.

Together with my colleagues on the committee, I will do my utmost to get industry back to the ISH - with their new cardio-metabolic and renal drugs as well as their new devices - and to make this again a "win-win" partnership for both sides.

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COMMITTEE REPORT MENTORSHIP AND TRAINING COMMITTEE

Creating opportunities for global mentoring and training

FRANCINE MARQUES

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The first description of the power of mentoring comes from the ancient Greek poem called Homer's Odyssey. In the poem, the Goddess of Wisdom Athena disguised herself as 'Mentor' to provide courage and wisdom to Odysseus' son, Telemachus. Centuries later, research now supports that mentoring is a powerful catalyst to unleash potential in science and medicine.1 This was acknowledged by the ISH, who established a mentoring program in the early 2010s and formally established a committee solely dedicated to mentoring in 2017: the Mentoring and Training Committee (MTC).

I have a deep appreciation for the impact mentoring has had on my own career development. As such, it was an honor to be appointed as chair of the MTC in 2019. Prior to my role as chair, I acted as a member of the MTC for 3 years and a member of the New Investigator Committee (NIC) Recruitment Working Group for another 4 years. I am an Associate Professor and molecular geneticist at Monash University, Australia. I lead a multidisciplinary team that specialises in understanding the role of the gut microbiota to blood pressure regulation,[2] from experimental studies[3] to randomized clinical trials.[4]

The MTC members share a passion about mentoring. The MTC includes Dr Augusto Montezano from the University of Glasgow (the UK), Dr Cameron McCarthy from the University of South Carolina (the USA), Dr Lebo Gafane-Matemane from the North-West University (South Africa), Dr Rodrigo Marañón from the National University of Tucuman (Argentina), Dr Zhiyi Ma from the Peking University People's Hospital (China), and Professor Prabhakaran Dorairaj, Director of the Centre for Chronic Disease Control (India). Together we represent early, mid- and senior-career stages, several minority groups, and all continents (Figure).

As a committee, we acknowledge the impact of the SARS-COV-2 pandemic on cardiovascular research and researchers.[5] Our major goal is to support the ISH community through these difficult times by providing outstanding mentoring and training resources. Since our committee was formed in 2020, we have leveraged online opportunities to expand and improve traditional MTC activities, such as the mentoring program, as well as develop new activities. These include several ongoing activities:

Mentoring program (Leads: Dr Lebo Gafane-Matemane and Dr Cameron McCarthy): Mentees are leveraging online communications to engage more frequently with their mentors. All seeking a mentor are welcome to apply here.

Mentoring training (Lead: Dr Lebo Gafane-Matemane): Besides developing a mentoring handbook to support mentees, the first Mentoring Scheme Seminar Series, aimed at empowering mentees to define their mentoring vision and thrive in their mentoring relationships, will take place online on the 30th of November.

Podcasts (Leads: A/Prof Francine Marques and Dr Augusto Montezano): Available on Spotify and Apple Podcast, we have now interviewed 12 leaders and emerging leaders from the hypertension community about their career path, advice on mentoring and ways to improve diversity and inclusion. These podcasts contain practical and inspiring advice, and are highly recommended for trainees and ECRs in particular.

Regional collaborations (Lead: A/Prof Francine Marques): We have now set up collaborations with regional societies such as the Brazilian Society of Hypertension (in collaboration with the New Investigator Committee), the High Blood Pressure Research Council of Australia (HBPRCA), and Hypertension Canada, and we hope to engage with further regional societies to provide more opportunities for junior researchers.

Training Seminar Series (Lead: Dr Rodrigo Marañón, in collaboration with the Women in Hypertension Research Committee): Launching on the 3rd of September with 'Sex Differences in Hypertension', the Training Seminar Series aims to offer learning opportunities with world-experts and celebrate research that is diverse and inclusive.

Mentoring survey (Lead: A/Prof Francine Marques): We believe mentoring is even more impactful for those who have the biggest barriers to success. Thus, we have designed a survey (pending approval) to determine the relationship between mentoring, diversity, and success in research.

Asia engagement (Lead: Dr Zhiyi Ma, in collaboration with the Communications Committee): We are devising new ways to communicate and engage with our members and colleagues in China, so our activities can have maximum reach.

We would like to thank the support of the Council, Dylan Burger (Chair of the Communications Committee), Muscha Steckelings (Chair of the Women in Hypertension Research Committee), Brandi Wynne (Chair of the NIC), and the Helen Horsfield (Executive Assistant). We believe these activities will improve the outreach of the ISH and have a positive impact in our global community members.

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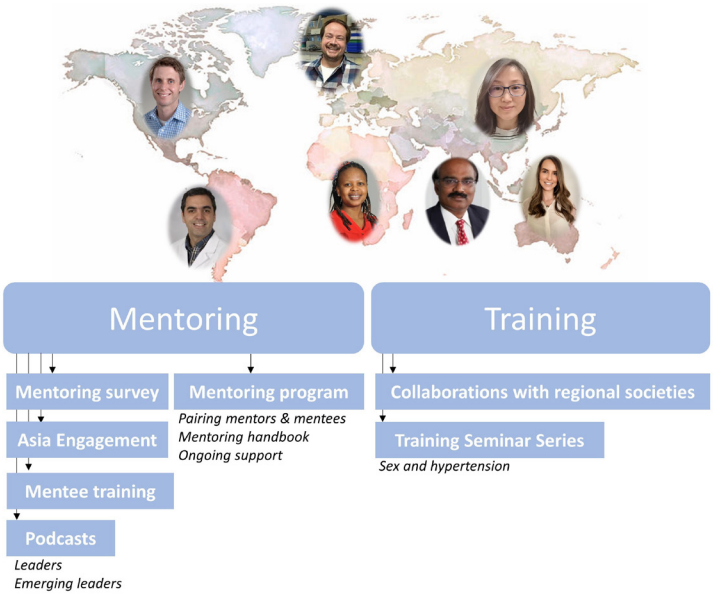

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Putting the evidence into clinical practice – the 2021 ESH Position Statement on Renal Denervation

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The first report on the safety and efficacy of catheter-based renal denervation (RDN) was published more than a decade ago [1] and informed by robust physiolgic evidence from both experimental and human studies highlighting the crucial contribution of renal nerves to blood pressure control via three major mechanims including modulation of renal blood flow, sodium and water retention, and renin release. Targeting the renal nerves via catheter-based approaches could perhaps be considered the interventional equivalent of a "polypill" composed of a vasodilatory agent, a diuretic, and a direct renin inhibitor. While the concept of RDN as a means of lowering blood pressure is undoubted, demonstrating the clinical efficacy of catheter-based RDN has been somewhat of a rocky road owing to pitfalls relating to achieving a circumferential ablation pattern with first generation catheters, patient selection, non-adherence with concomitantly prescribed medication, and others. As a consequence, the ESH/ESC hypertension guidelines published in 2018 recommended the use of renal denervation only in the context of clinical studies but not for routine treatment of hypertension, at least until further randomized clinical trial (RCT) evidence is available to demonstrate both the safety and BP lowering efficacy.

Several years down the track with learnings from previous studies incorporated into study designs including use of ambulatory BP measurement, assessment of adherence with concomitantly prescribed antihypertensive medications from blood or urine samples, use of next generation technologies facilitating circumferential ablation with either radiofrequency energy or therapeutic ultrasound, and others, five sham-controlled RCTs in either drug-naïve or treated patients with hypertension [2-6] have now reported with each demonstrating a favourable safety profile with significant and clinically relevant BP lowering efficacy as summarized in Figure 1.

Further supported by meta-analyses of available RDN studies, the ESH Working Group on Device-Based Treatment of Hypertension very recently published a position statement on RDN to summarize the current evidence on safety, efficacy and durability, provide a pathway of how to implement RDN in clincal practice, and identify open questions that need to be addressed [7].

In brief, the position statement highlights RDN as an evidence-based option to lower BP as a complementary approach to lifestyle modification and pharmacotherapy. The various endovascular procedures tested in RCTs [2-6] are safe with absence of significant short-term or longer-term adverse effects up to 3 years. A structured approach for implementation into clinical practice is critical and includes relevant qualification of centres and operators performing RDN, capacity for comprehensive diagnostic workup and structured follow up of patients undergoing RDN, and most importantly, involvement of the patient in shared decision process taking patient preference into account (Box 1).

Having a third pillar in our armamentarium to lower BP may help to improve the stubbornly poor control rates of hypertension.

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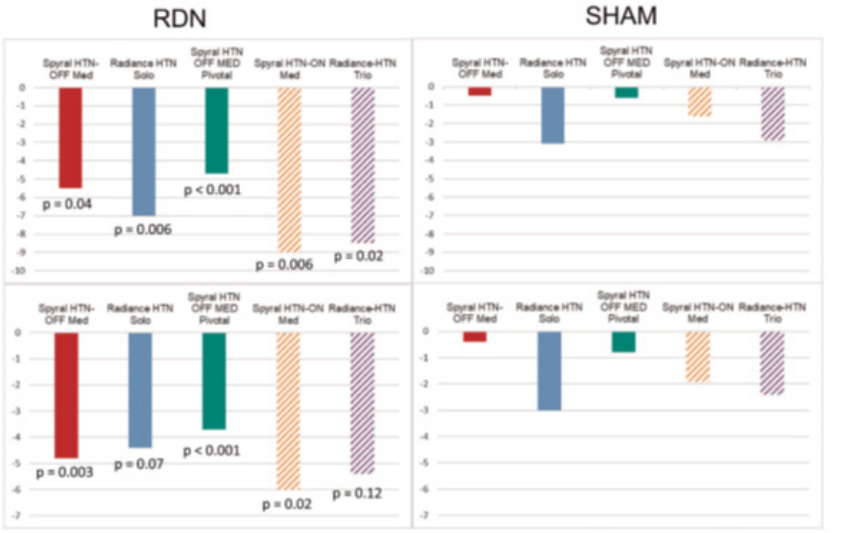

Figure 1: Changes in 24-h ambulatory systolic (top panels) and diastolic (bottom panels) after renal deneva-tion (RDN) (left panels) or a sham procedure (right panels). (with permission from reference 7).

BOX 1: Position Statement in 2021

- On the basis of consistent results of several sham-controlled clinical trials, renal denervation represents an evidence-based option to treat hypertension, in addition to lifestyle changes and blood pressure lowering drugs.
- Renal denervation therefore expands therapeutic options to address the first objective of hypertension treatment, that is to effectively reduce an elevated blood pressure and achieve blood pressure targets.
- Renal denervation is considered a safe endovascular procedure without significant short-term or long-term adverse effects based on data available up to 3 years.
- Renal denervation is an alternative or additive, not a competitive treatment strategy.
- A structured pathway for clinical use of RDN in daily practice is recommended.
- Patients' perspective and preference as well as patients' stage of hypertensive disease including comorbidities should lead to an individualized treatment strategy in a shared decision-making process, that carefully includes the various options of treatment, including renal denervation.

Box 1:

Summary of major recent findings and recommen-dations (with permission from reference 7)

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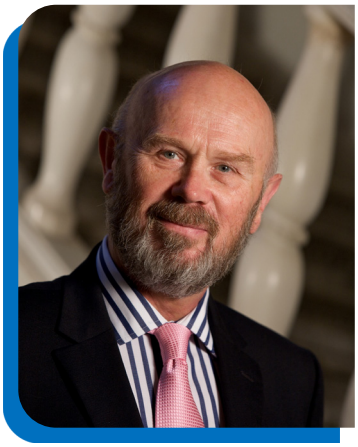
COMMITTEE REPORT

May Measurement Month Campaign Continues Its Vital Work



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May Measurement Month (MMM) is the annual global blood pressure (BP) screening campaign initiated by the International Society of Hypertension (ISH), which aims to raise awareness of the importance of measuring BP and helps people to get their blood pressure (BP) checked. Due to the COVID-19 pandemic, MMM was cancelled in 2020 but it is well underway with its extended 2021 programme of screenings.

Despite COVID-19, 94 countries are taking part this year, an increase of the previous campaigns which together screened over 4.2 million adults globally. In the three previous campaigns over one million people with untreated, or poorly managed hypertension were detected.

Restrictions due to COVID-19 make BP screening variably challenging in all countries taking part in MMM this year. However, the MMM coordinators have been extremely careful to support each participating country in ensuring that local and national government guidelines are being carefully followed and implemented.

It remains to be seen to what extent these challenges will impact the number of screenees taking part this year.

Where normal face to face screening is not suitable or possible, we introduced a home screening protocol for MMM21 and this has been significant uptake, with guidance re measurement made available on the MMM website (https://maymeasure.org) for participants. Plans are also in place to collect home BP data from participants in UK contributing the huge ZOE COVID symptom Study App.

MMM teams in the Philippines and Georgia have also been working with local vaccination centres to screen participants during their attendance for COVID-19 vaccinations.

MMM data will be investigated both retrospectively from the three previous campaigns and prospectively in MMM21 to evaluate the association between air pollution and BP levels. The latter will be based on data collected in 12 cities across five South East Asian Countries – Philippines, Malaysia, Indonesia, Vietnam and Thailand.

The MMM Management Board are also very pleased to announce that its longstanding partnership with OMRON, has been renewed for the next four years, and will now include providing the MMM campaign with a further 20,000 BP machines and over 1,100 devices which incorporate a single lead ECG to detect atrial fibrillation alongside the standard BP measurement.

A series of analyses of MMM data are in progress or were recently completed to allow the generation of publications on the association between MMM BP parameters and altitude temperature, time of day, BP variability, pregnancy associated hypertension, and national stroke mortality.

These imminent publications highlight the availability of the MMM database for those ISH members who wish to pursue any areas of their interest which are incorporated in the MMM database.

Finally, the third MMM supplement, including 47 national publications from 2019, is now available online at via the Oxford University Press website. For more information about how you can support, visit www.maymeasure.org

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COMMITTEE REPORT

Upcoming and Recent events by Women in Hypertension Committee

MUSCHA STECKELINGS, NIAMH CHAPMAN, MANSI PATIL

The ISH Women in Hypertension Research Committee (WiHRC)

The ISH Women in Hypertension Research Committee (WiHRC) has been established to encourage, support and inspire women in science and medicine in the field of hypertension and related cardiovascular diseases. It aims to establish new avenues for communication, collaboration and education.

Women are pursuing STEM jobs at careers at never-before-seen rates, and this growing presence of female voices is tremendously inspirational. The academic community has not yet resolved all of the challenges that women encounter, and much more work remains. One issue that women are typically facing is that a sense of belonging and support structures are lacking[1]. The necessity for promoting women, involving them and creating an ecosystem for women to enter and continue research in cardiovascular diseases is the need of the day. It is imperative that we create opportunities for interaction and knowledge dissemination to encourage more women to become a part of this network.

This spring, the WiHRC has founded the Women in Hypertension Research Network to create a community of women, to encourage them, and offer opportunities to advance their career. The WiHR Network is open for all ISH members. Over the past few months, the committee and network members have strived to reach all parts of the world and contribute to various events, conferences and activities. These included collaborations for talks, interviews, workshops and community screening for hypertension.

Recent Activities by the WiHRC

Launch of the WiHR Network on 14th April 2021 at the ESH/ISH joint conference moderated by Niamh Chapman and Guto Montezano. The need for visible role models, mentors and support networks were common themes to support women's career progression as well as a need to call out behaviour that disadvantages women in research.

Session on Career Development at the ESH/ISH Joint conference April 2021 (virtual). Muscha Steckelings, Nadia Khan, Rhian Touyz and Mansi Patil discussing challenges and successes in female early, mid and senior careers.

Hypertension in Pregnancy session at the ESH/ISH Joint conference April 2021 chaired by Lizzy Brewster and Siew Mooi Ching

Nutrition and Hypertension session at the Hypertension and Nutrition Core Group, IAPEN India Association for Parenteral and Enteral Nutriton (virtual) with Pensee Wu and María S. Fernández-Alfonso as speakers and Mansi Patil as Chair.

Heart health talk during the Australian Heart Week organised by Niamh Chapman and with Alta Schutte as guest.

May Measurement Month 2021 blood pressure screening initiative in Ghana coordinated by Betty Owusu Ansah

15th Oriental Cardiology Conference/Hypertension Forum, China (virtual) with Yan Li, Muscha Steckelings and Mansi Patil as Chairs and discussants and Lizzy Brewster as speaker.

ISHLive organised by the ISH New Investigators Committee with Audrey Adji as WiHRC representative (March 25, 2021)

ISHLive organised by the Mentorship and training Committee with Mansi Patil from the WiHRC (15th August 2021)

Career development session at the Meeting of the Brazilian Society of Hypertension (August 7th 2021, virtual) with participation of the ISH Mentoring and Training Committee (Mariane Bertagnoli, Francine Marques, Guto Montezano) and the WiHRC (Muscha Steckelings)

ISH Training Seminar on "Sex Differences in Hypertension" organised by the ISH Mentoring and Training Committee on September 3rd (virtual) with participation of the WiHRC (Lizzy Brewster, Anne Monique Nuyt, Pensée Wu, Muscha Steckelings)

Virtual meeting of the Pakistan Hypertension Society on 13th September 2021 on "Risk factors of Hypertension in Women" with participation of the WiHRC (Muscha Steckelings, Niamh Chapman, Anastasia Mihailidou and Yan Li).

Upcoming events by the network

1. Session on "Women and Hypertension" at the Chinese Hypertension Meeting, Sept 25, 2021, with participation of Yan Li, Audrej Adji and Muscha Steckelings

2. Session at the meeting of the European Council for Cardiovascular Research (ECCR) on Oct 8 and 9 (https://eccr.org/)

3. 30 minutes online mentoring meetings by Zoom with 11 mentors available for open-topic conversations with junior ISH members (October 11 and 22).

For more details see the WiHRC Newsletter: https://ish-world.com/wp-content/uploads/2021/07/WIHRC-Newsletter-July-2021.pdf

Membership in the Women in Hypertension Research Network is free for all ISH members.

If you are interested to join, contact the secretariat (secretariat@ish-world.com) or write to us: WiHRC@ish-world.com

Also check out our webpage: https://ish-world.com/women-in-hypertension

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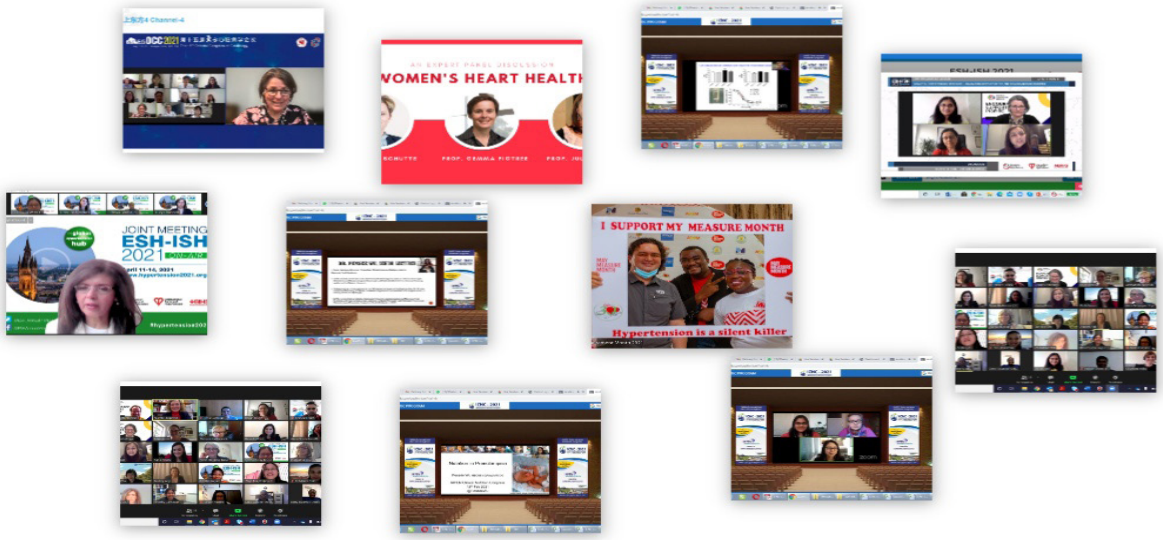

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LET'S REDUCE DISPARITIES IN THE MANAGEMENT OF HYPERTENSION.

Hypertension remains the leading global cause of cardiovascular disease and preventable death.[1] Low- and middle-income countries have more people with hypertension than high-income countries and lower rates of blood pressure control.[2]

These disparities vary significantly according to ethnicity and genetic differences, and are accompanied by lower levels of awareness, treatment, and control.[3]

Read the **2020 International Society of Hypertension Global Hypertension Practice Guidelines** to learn how to start addressing the needs of hypertensive patients worldwide.

ish-world.com

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Program focused on 1. Food 2. Moving 3. AI

Your proposal is always welcome at " www.ish2022.org "!!

Activity of the Japanese Society of Hypertension (JSH)

JSH Plan for the Future
Good Blood Pressure for Lively 100 Years

Reduce hypertensive patients by 7 million in 10 years, and Expand the healthy life expectancy
Through…

1 Medical System — Establish a lifetime-care system for individuals with hypertension
2 Academic Research — Promote research in hypertension and embody "Future Medicine"
3 Social Edification — Develop a social model for self-controlled blood pressure

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